ORIGINAL ARTICLE

Intisari Sains Medis 2021, Volume 12, Number 1: 187-191
P-ISSN: 2503-3638, E-ISSN: 2089-9084

Intisari Sains Medis

Published by Intisari Sains Medis

Correlation of glutamine and serial absolute neutrophil count as a parameter of infection in major burn trauma patients at Sanglah General Hospital, Bali, Indonesia

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Received: 2020-12-17
Accepted: 2021-03-28
Published: 2021-04-22

ABSTRACT

Background: Burns are thermal trauma that often results in high morbidity. In major burns, gastrointestinal dysfunction plays a vital role in the progression of infection to organ failure. Glutamine is a pharmaconutrient that has important implications for burn patients, including in the prevention of infection. This study evaluates the relationship between glutamine administration and the serial absolute neutrophil count as a parameter for infection incidence in patients with major burns.

Methods: This study was an analytical study with a cross-sectional design to see the relationship between glutamine administration and the serial absolute neutrophil count levels of major burn patients at Sanglah General Hospital. The sample consisted of 56 patients from the medical records of burn patients. The data were extracted from the medical records and then inserted into the data collection sheet. Then performed data analysis using SPSS version 21 for Windows.

Results: Bivariate analysis showed that there was a significant difference between glutamine administration and the absolute neutrophil count levels on days 3, 5, and 14 ($p = 0.004$, 95% CI: 1.70-8.46), ($p = 0.000$, 95% CI: 2.71-7.83), and ($p = 0.035$, 95% CI: 0.61-7.27), respectively. This showed that patients given glutamine had lower neutrophil levels on days 3, 5, and 14 than patients who were not given glutamine. Multivariate analysis confirmed that glutamine administration did independently affect and decrease the absolute neutrophil count levels on days 3, 5, 14, and the mean without being influenced by other variables with p value = 0.004 (95% CI: [-8.445] - [-1,732]), $p = 0.000$ (95% CI: [-7,808]-[-2,743]), $p = 0.020$ (95% CI: [-7.251]-[-0.639]), and $p = 0.017$ (95% CI: [-5,815]-[-0.588]), respectively.

Conclusion: This study has shown that glutamine administration was significantly associated with and decreased the serial absolute neutrophil count in major burn patients.

Keywords: Glutamine, Absolute Neutrophil Count, Severe Burn Injury.
Cite This Article: Sudarsa, S.D., Hamid, A.R.R.H., Harimawan, A.I.W., Budayanti, N.N.S. 2021. Correlation of glutamine and serial absolute neutrophil count as a parameter of infection in major burn trauma patients at Sanglah General Hospital, Bali, Indonesia. *Intisari Sains Medis* 12(1): 187-191. DOI: 10.15562/ism.v12i1.890

INTRODUCTION

Burns are thermal trauma that often produces significant morbidity and cause impaired emotional well-being and quality of life. Burns require immediate intensive care as well as long-term care and sometimes require reconstructive surgery with or without hospitalization.[1] These burns' health-related consequences are often accompanied by additional socio-economic burdens for the burn victim and their family.[1]

Burns did not cause death, but it is a significant cause of morbidity, increased duration of hospitalization, and disability, impacting psychological, social, and economic effects.[1,2] In 2004, nearly 11 million people in the world experienced burns requiring hospitalization. About 80% of burn cases occur at home.[2] The frequency of death due to burns in countries with low and middle incomes eleven times higher than in high-income countries. Most deaths from burns also occur in Africa, Southeast Asia and the Middle East, with about 195,000 people dying from these events each year.[2] The prevalence of burns in Indonesia is 0.7%. The highest prevalence occurs at the age of 1 year to 4 years of 1.5%.[2]

The burn condition readily induces a more severe inflammatory tissue response such as bulla formation or cystic swelling.[2] Burns are classified into three degrees based on the depth, which is first degree with superficial burns, second degree if the burn's depth is partial, and third-degree if it is full thickness.[3] According to Bruck et

al., there is a secondary fungal infection in 17% of patients with second-degree burns.[4] On the other hand, the risk of bacterial infection is even higher. Besides, both acute and chronic inflammation in burns can cause several complications related to burns, including local complications. (eschar, scar tissue, and contractures) or systemic, which often manifests as metabolic changes (hyperglycemia) and hypovolemia or electrolyte disturbances.[5]

In severe burn injuries, gastrointestinal dysfunction plays a vital role in developing an infection, the course of sepsis, and even organ failure.[5] Recently published studies have shown that intestinal ischemia/reperfusion plays an important role in initializing and maintaining reactive oxygen species, leukocyte priming, and inflammatory mediators.[6,7] Recent data show that gastrointestinal tract-derived factors can appear in the systemic circulation through the lymph system instead of originating from the portal vein and cause multi organ failure.[6,7] Additionally, they contribute to organ dysfunction and lead to infection as they decrease immune function.

Glutamine is a pharmaceutical nutrient that has important implications for burn patients. Patients with burns have decreased glutamine levels and low levels of glutamine in the blood are associated with critical illness with poor clinical outcomes.[6] Glutamine also plays a vital role in the intestine's normal immunological function and structure because enterocytes prefer glutamine as a substrate. Experimental laboratory studies show that glutamine deficiency leads to loss of intestinal epithelial barrier function.[8] Glutamine supplements are able to reduce mucosal atrophy in the intestines during parenteral nutrition (PN), maintain extra- and intraintestinal levels of immunoglobulin A, prevent peyer patch-related glutathione loss, and do not increase nitric oxide production via inflammatory cytokine generation.[8,9]

This study evaluates the relationship between glutamine administration and the serial absolute neutrophil count as a parameter of infection incidence in patients with major burns. This study's results are expected to confirm the position of glutamine as a potential prognostic factor in burns, particularly major burns.

Table 1. Baseline characteristics of research subjects

Variable	Glutamine (N=56)	
	Not-Received Glutamine (N=28)	Received Glutamine (N=28)
Age (Years) (Mean±SD)	37.36 ± 18.56	39.36±16.28
Gender, n (%)		
Female	5 (29.40)	12 (70.60)
Male	23 (59.00)	16 (41.00)
Percentage of Burns (%) (Mean±SD)	38.10±15.47	39.50±18.59
Grade of Burns, n (%)		
II	22 (46.80)	25 (53.20)
III	6 (66.70)	3 (33.30)
Location of Burn Trauma, n (%)		
Multi Region	18 (46.20)	21 (53.80)
Not Specific	2 (40.00)	3 (60.00)
Extremities	2 (50.00)	2 (50.00)
Head and Neck or Face	3 (75.00)	1 (25.00)
Body and Extremities	3 (100.00)	0 (0.00)
Body	0 (0.00)	1 (100.00)
Absolute Neutrophil Count (10^3/uL) (Mean±SD)		
Day 1	19.76±10.14	21.26±9.77
Day 3	17.05±7.77	11.96±4.24
Day 5	15.51±6.04	10.24±2.86
Day 14	13.90±7.56	9.95±4.34

METHODS

This research was conducted at Sanglah General Hospital Denpasar, Bali, from September to November 2020, with a total sample of 56 people. The sample of this study was a sample from the medical records of patients at Sanglah General Hospital regarding the basic characteristics of the patient, including name; age; grade of burns; location of burns; percentage of burns, levels of glutamine administration; absolute serial levels of neutrophil count on day 1, 3, 5, 14; and the presence or absence of complications or comorbidities. The target population in this study was all patients with second-degree burns with an area of ≥ 20% Total Body Surface Area (TBSA) in Bali, and the targeted population was patients with second-degree burns with an area of ≥ 20% TBSA who was treated at Sanglah General Hospital Denpasar.

This study used an analytical study with a cross sectional design to see the relationship between glutamine administration and the serial absolute neutrophil count in patients with major burns. The inclusion criteria in this study were patients with second-degree burns with an area of ≥20% TBSA who were hospitalized at Sanglah General Hospital Denpasar, aged 18-60 years and had received glutamine therapy. This study's exclusion criteria were patients with BMI <17, diabetes mellitus, history of vasoconstrictor used, systemic inflammation, immune-compromised, chemotherapy, malignancy or radiotherapy, venous dysfunction (varicose) in the burn area, and patient with incomplete medical record data. All data obtained were then analyzed using SPSS version 21 software for Windows.

RESULTS

The 56 samples were divided into two groups based on glutamine administration: patients who received glutamine administration and patients who did not receive glutamine consisting of 28 patients for each group (Table 1).

The mean age of the patients in this study was 38.36±17,328 years. Patients in the glutamine free group had a lower mean age (37.36 ± 18.56 years) than patients with glutamine (39.36±16.28). Furthermore, in terms of gender, the percentage of female patients is less than male patients. Based

Table 2. Bivariate analysis between glutamine administration and average absolute neutrophil count for major burn patients

Variable	Glutamine Administration (N=56)		MD	p	95% CI	
	No (N=28)	Yes (N=28)			Lower	Upper
Absolute Neutrophil Count (10^3/uL) (Mean±SD)						
Day 1	19.76±10.14	21.26±9.77	-1.500	0.574	-6.84	3.83
Day 3	17.05±7.77	11.96±4.24	5.088	0.004[a*]	1.70	8.46
Day 5	15.51±6.04	10.24±2.86	5.270	0.000[b*]	2.71	7.83
Day 14	13.90±7.56	9.95±4.34	3.940	0.035[b*]	0.61	7.27

SD: Standard Deviation; MD: Mean Difference; CI: Confidence Interval; a=Independent T-Test; b=Mann-Whitney U test; *Statistically significant if p-value less than 0.05

Table 3. Multivariate analysis between glutamine administration and average absolute neutrophil count for major burn patients

Variable	Unstandardized Coefficients		Standardized Coefficients Beta	t	95% CI		p
	B	SE			Lower	Upper	
Glutamine-Neu Day 3							
Constant	17.051	1.184	-0.382	14.403	14.677	19.424	0.000*
Glumatine Administration	-5.089	1.674		-3.039	-8.445	-1.732	**0.004***
Glutamine-Neu Day 5							
Constant	15.519	0.893	-0.494	17.372	13.728	17.310	0.000*
Glumatine Administration	-5.275	1.263		-4.176	-7.808	-2.743	**0.000***
Glutamine-Neu Day 14							
Constant	13.900	1.166	-0.310	11.921	11.562	16.238	0.000*
Glumatine Administration	-3.945	1.649		-2.392	-7.251	-0639	**0.020***
Glutamine-Average Neu							
Constant	16.557	0.922	-0.317	17.963	14.709	18.406	0.000*
Glumatine Administration	-3.201	1.304		-2.456	-5.815	-0.588	**0.017***

Neu: Neutrophils; SE Standard Error; B=Beta; CI: Confidence Interval; *Statistically significant if p-value less than 0.05

on gender, there were 5 patients (29.40%) who did not receive glutamine, while 12 patients (70.60%) received glutamine. On the other hand, there were 23 (59.00%) male patients who did not receive glutamine, while 16 patients (41.00%) received glutamine (Table 1).

Based on the analysis of the percentage of burns, patients who did not receive glutamine had an average burn rate of 38.10±15.47 percent, while in the group receiving glutamine, the average percentage of burns was 39.50±18.59 percent. The grade II burn analysis results showed that the majority of burn patients collected in this study were grade II burn patients. In the group that was not given glutamine, 22 grade II patients (46.80%) and 25 grade II patients received glutamine therapy (53.20%). Then in the group that did not get glutamine, there were 6 patients with grade III burns (66.70%), more than the grade III patients who received glutamine were 3 patients (33.30%) (Table 1).

This study indicates that the mean serial absolute neutrophil count levels of major burn patients vary depending on the day of observation. On the first day, the mean of the group that did not receive glutamine was lower than the group receiving glutamine (19.76±10.14 vs. 21.26±9.77). On the third day, the average glutamine level in the group that did not get glutamine was higher than the group that received glutamine (17.05±7.77 vs. 11.96±4.24). Similar results were also found on the fifth and fourteenth-day observations, where the average group that did not get glutamine was higher than the group that received glutamine (day 5: 15.51±6.04 vs. 10.24±2.86; day 14: 13.90±7.56 vs. 9.95±4.34) (Table 1).

Bivariate analysis was performed using the Independent T-Test on normally distributed data and the Mann-Whitney test on data that were not normally distributed. This test is useful for comparing the number of neutrophils in two groups of patients (with glutamine and without glutamine). On the first day, the absolute mean neutrophil count was greater in the glutamine treated group of patients than the non-glutamine group with a mean difference of -1.50. On the third day, there was a difference in the mean neutrophil count of 5.088. On the fifth day, there was a difference in the mean neutrophil count between groups was 5.27. Meanwhile, on the 14th day, the mean neutrophil count difference between groups was 3.94 (Table 2).

The results of the Independent T-Test analysis on the first day showed that there was no statistically significant difference in the mean neutrophil count between the groups given and not given glutamine (p=0.574, 95%CI: [-6.84]-[3.83]). Meanwhile, the Independent

T-Test results on the third day showed a statistically significant difference in the mean neutrophil count between the groups given and not given glutamine (p=0.004, 95%CI: 1.70-8.46) (Table 2).

The Mann-Whitney analysis results were carried out on the absolute number of neutrophils on day 5 and day 14 because of the abnormal data distribution. On day 5, there was a p-value <0.001 (p=0.000, 95%CI: 2.71-7.83), which indicated a statistically significant difference in the mean neutrophil count between the groups given and not given glutamine. Likewise, the Mann-Whitney test results on day 14 showed a statistically significant difference in the mean neutrophil count between the groups given and not given glutamine (p=0.035, 95%CI: 0.61-7.27). This mean difference is statistically significant because the p-value is less than 0.05 (Table 2).

In order to further evaluate the relationship between glutamine administration and the serial absolute neutrophil count levels, a multivariate analysis was carried out to see the independent effect of glutamine administration on the absolute neutrophil count levels on days 1, 3, 5, and 14. Since all the variables tested were numerical variables, linear regression is used in this phase. From the analysis, it was found that glutamine administration was significantly associated with the serial absolute neutrophil count levels on days 3, 5, 14, and the mean absolute neutrophil count with Beta was -0.382 (95%CI: [-8.445]-[-1,732]; P=0.004), -0.494 (95%CI: [-7,808]-[-2,743]; P=0,000), -0.310 (95%CI: [-7,251]-[-0.639]; P=0.020), and -0.317 (95%CI: [-5,815]-[-0.588]; P=0.017), respectively (Table 3). This shows that glutamine administration independently affects and reduces the serial absolute neutrophil count levels without being influenced by other variables.

DISCUSSION

Severe burn trauma can cause changes in neutrophils' circulating function, including the impaired ability of neutrophils to migrate to the site of infection and decreased ability to kill microorganisms.[7] In burn patients with infection, there was a significant increase in the number of neutrophils in the white blood cells count at 1, 3, and 5 days after the burn. Burns will stimulate changes in hematopoiesis by inducing an acute phase response so that neutrophils can be an important indicator in evaluating burns.[7] A previous study found that patients without burns had neutrophil levels of 65.53 ± 6.08%, 1-day post-injury burns patients had neutrophil levels of 82.11 ± 6.84%, 3 days post-injury burn patients had neutrophil levels of 74.89 ± 6.77%, whereas in patients burns 5 days post-injury had neutrophil level is 76.44 ± 5.76%.[10]

The level of neutrophils as an indicator of infection in burn patients can be decreased by administering glutamine to reduce infection incidence.[11,12] In general, glutamine has a function in preventing burn-related myocardial injury, maintaining muscle metabolism by increasing insulin sensitivity, increasing protein synthesis, and enhancing the healing process of wound tissue, as well as protecting cells from damage by triggering increased expression of heat shock protein (HSP), maintaining expression level of Growth Stimulating Hormone (GSH).[11,12] Glutamine is used to synthesize malate which is used to produce NADPH in burn cases. NADPH is essential to synthesize superoxide anion (O_2-), which will eradicate microcircuits to decrease infection incidence.[13] Besides, it was found that in burns, glutamine has a major role as a nutrient needed to reduce apoptotic levels in Peyer's patches due to severe burns.[12]

The level of glutamine used by all cells becomes equal to or greater than glucose use during infection or high catabolic conditions.[14,15] However, the increase in the use of glutamine by immune cells is in accordance with the increase in the use of amino acids by other tissues, such as the liver, so that glutamine deficiency can occur in the human body.[15] Glutamine deficiency will cause functional changes in some immune cells. For example, glutamine plays a role in controlling immune cell proliferation by activating proteins, such as ERK and JNK kinases.[15,16] Both proteins act on the activation of transcription factors, such as JNK and AP-1, and lead to the transcription of genes associated with cell proliferation. For example, glutamine concentrations that lead to lymphocyte cells surface markers, such as CD25, CD45RO, and CD71 related to the production of cytokines, such as interferon-gamma (IFN-γ), TNF-α, and IL-6.[16] Thus, glutamine acts as an energy substrate or modulator for leukocytes and plays an important role in cell proliferation, the activity of tissue repair processes, and the intracellular pathways associated with pathogen recognition.[17]

As a conditionally essential amino acid in burns, glutamine can activate peroxisome proliferator-activated receptor (PPAR) DNA binding and suppress the inflammatory response through the nuclear factor-KB (NFkB) signaling pathway.[18] Glutamine is said to have no effect on neutrophil phagocytosis in burns. However, glutamine can increase neutrophils' bactericidal activity through other mechanisms such as increasing the formation of reactive oxygen metabolites and increasing neutrophil degranulation.[19] Glutamine supplementation has shown a reduction in translocation from bacterial infections in experimental animals that have burned.[12] It serves to maintain the decreased ATP levels in burns and shock, causing apoptosis in cells, and plays a role in preventing apoptosis in lymphocytes which play an immune function in burns, and increases the survival of experimental animals that experience burns.[12]

The RCT study conducted by Wischmeyer PE et al., showed that by providing parenteral glutamine 0.5 g/kgBW/day found a statistically significant reduction in the incidence of infectious complications (RR 0.86, 95%CI 0.73-1.02, P=0.09), as well as a reduction in mortality (RR 0.68, 95% CI 0.51, 0.90, P=0.008).[20] A similarity to the RCT design was found in the previous studies by Bollhalder L et al., and Stehle P et al.[21,22] In line with this study, it was found that the role of glutamine was statistically significant in reducing the incidence of infection on days 3, 5 and 14 as measured by serial neutrophil levels with p-value (P=0.004; 95%CI: [-8.445]-[-1,732]), (P=0.000; 95%CI: [-7,808]-[-2,743]), (P=0.020; 95%CI: [-7.251]-[-0.639]) for day- 3, 5, and 14, respectively. A previous meta-analysis study of glutamine administration in burns showed a statistically significant benefit in

terms of reduced mortality (risk ratio [RR] 0.22, 95%CI 0.07, 0.62, P=0.005); however, results were found to be contradictory to the incidence of infection (RR 0.78, 95%CI 0.46, 1.31, P=0.34, 3).[6,23]

Apart from being important in administering glutamine, administration timing is also a factor that needs to be considered. Substantial damage to the intestinal mucosa and increased bacterial translocation in burns reduce nutrient absorption. Therefore, nutritional supplementation should ideally be initiated within 24 hours of experiencing burns using the enteral route.[24] In animal studies, trials of enteral feeding at baseline were shown to reduce the hypermetabolic response after severe burns significantly.[24] A study by Mochizuki H et al., Demonstrated that guinea pigs that were fed enterally continuously starting 2 hours after burn had a significant reduction in metabolic rate at 2 weeks after burns compared to animals whose nutrition was started 3 days after-burn.[25]

CONCLUSION

This study concludes that glutamine administration is significantly associated with and decreases the serial absolute neutrophil count levels in patients with major burns. Further study with bigger sample size and cohort design study is recommended for future studies to determine causal effect between glutamine and serial absolute neutrophil count as a parameter of infection in major burn trauma patients.

ETHICAL CLEARANCE

Ethics approval was obtained by the ethics commission, Faculty of Medicine, Udayana University, Sanglah General Hospital, Bali, Indonesia, before this research was carried out.

CONFLICT OF INTEREST

There is no conflict of interest in writing this research.

FUNDING

The author is responsible for funding this research without involving grants, sponsors, or other funding sources.

AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data gathering, data analysis, until reporting the results of study through publication.

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