

The effect of Aloe vera syrup on prevention of fever and neutropenia in children with acute lymphoid leukemia

Azam Sadat Hashemi MD^{1,*}, Maliheh Kokab MD¹, Masoud Kamalian MD², Mohammad Zarezadeh PhD³, Elnaz Sheikhpour PhD¹, Leila Azod BSc⁴, Tahereh Fallah BSc⁵

1. Hematology and Oncology Research Center, Shahid Sadoughi hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

2. Department of Radiology, Shahid Sadoughi hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

3. Health Policy and Management Research Center, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

4. Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

5. Shahid Sadoughi hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

*Corresponding author: Dr. Azam Sadat Hashemi, Hematology and Oncology Research Center, Shahid Sadoughi hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Email: drazamhashemi@yahoo.com. ORCID ID: 0000-0003-4468-5884.

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Abstract

Background: Given that few studies regarding the effect of Aloe vera (A. vera) on prevention of fever and neutropenia on acute lymphoid leukemia (ALL) disease, the aim was to evaluate the effect of A.vera on prevention of fever and neutropenia in children with ALL.

Materials and Methods: This randomized clinical trial study was conducted on 60 children with mean age 5.6±2.9 years in Oncology department of Shahid Sadoughi hospital during 2018-2019. All these children were underwent chemotherapy. Then, the patients were randomly classified into two groups. The first group received 10 ml A. vera syrup (0.5 mg/ml) for 30 days (case group) and the second group did not receive A. vera syrup (control group). Complete blood count (CBC) tests and frequency of fever, infection, neutropenia, and hospitalization were evaluated in case and control groups before and after intervention. Wilcoxon, T test, and Chi Square test were used for data analysis.

Results: Significant reduction was observed in case group in comparison with control group regarding the frequency of fever (0.19 ±0.107 vs 1.07±0.206), infection (0.81 ±0.2 vs 1.87± 0.236), hospitalization (0.37±0.178 vs 1.33 ±0.187), and neutropenia (0.11± 0.062 vs 0.80 ± 0.2) (p<0.01). Moreover, significant increase was observed in case group in comparison with control group considering neutrophil count (2597.5±243.1 vs 1106.53±161.6) and white blood cell (WBC) (4062.96 ± 276.6 vs 2566.67 ±175.5) (p<0.01). In addition, recovery of appetite was significantly greater in case group than control group (p=0.023). Furthermore, significant difference was observed in case group before and after intervention regarding these parameters (p<0.05).

Conclusion: According to findings, A. vera consumption decreased frequency of infection, neutropenia, fever, and hospitalization and increased WBC and neutrophil count. Moreover, appetite was improved in these patients. Therefore, it seems that A.vera can be used for improving quality of life in children with ALL.

Keywords: Acute lymphoid leukemia, Aloe vera, Fever, Neutropenia

Introduction

Leukemia is the main cancer in the body's blood-forming tissues (1-3). Acute lymphoblastic leukemia (ALL) is the most prevalent type of leukemia among children (2, 3). The incidence peak of ALL in children is in age range of 2-5 years old. About 6000 new cases of ALL are

diagnosed annually in the United States (1,4,5). This disease occurs due to interaction of endogenous and exogenous and genetic susceptibility (1).

The survival rate of ALL children in the world has been improved approximately 90 % (1, 5). A main complication after intensive chemotherapy in children with

ALL is febrile neutropenia (6). The majority of infections in febrile neutropenia are due to fungal and bacterial infections (7). Viral infections are responsible for 34 % of proven infections in febrile neutropenia (7). There is a significant difference between countries, regions, and centers in terms of involved microorganisms in the etiology of febrile neutropenia (8). Treatment of febrile neutropenia by efficient drugs reduces morbidity and mortality (1). On the other hand, appropriate initiation of therapies have main role in febrile neutropenia attacks (6). Recently, the use of medicinal herbs as a medicinal and nutritional supplement for improving general health and treatment of diseases has taken into consideration (9). Aloe vera (*A. vera*) plant is originated from arid climates of North Africa (10). It is a succulent cactus like perennial plant with 275 species worldwide. Antiviral, antifungal, and anti-neoplastic activities of *A. vera* are specified in studies (10). Moreover, *A. vera* is used against bacteria, including *Pseudo-monas*, *Escherichia coli*, *Salmonella*, *Staphylococcus*, *Streptococcus*, *Klebsiella*, *Pseudo-monas*, etc. In addition, *A. vera* can have a significant role in the improvement of neutropenia-induced fever as one of the major complications after chemotherapy due to its strong stimulatory effects on the immune system and anti-inflammatory effects (11). Given the high prevalence of ALL in Iran, especially Yazd province(1), the use chemotherapy as the first line of treatment and few studies in this regard, the aim of current study was to evaluate the effect of *A.vera* syrup on prevention of fever and neutropenia in children with ALL referred to pediatric oncology ward of Shahid Sadoughi hospital.

Materials and Methods

This randomized clinical trial study was conducted 60 children hospitalized in Oncology department of Shahid Sadoughi hospital, Yazd, Iran, during 2018-2019.

These children were underwent chemotherapy with a treatment protocol. After taking consent from parents of children, this study was approved by Shahid Sadoughi University of Medical Sciences (number: IR.SSU.MEDICINE.REC.1396.187). Then patients were randomly classified into two groups. The first group (group 1) received 10 ml *A. vera* syrup (0.5 mg/ml) for 30 days (case group) and the second group (group 2) did not receive *A. vera* syrup (as control group). Complete blood count (CBC) tests were done by Sysmex cell counter (k-21, Japan) in all patients. Moreover, parameters such as frequency of fever, infection neutropenia, and hospitalization were evaluated in case and control groups. Moreover, these parameters were assessed before and after intervention. Children's appetite was assessed in all patients.

Statistical analysis

Data were entered SPSS, version 19. Wilcoxon Test, T test, and Chi Square test were used for analysis of data. $P < 0.05$ was considered statistically significant.

Results

The mean age of patients in case and control groups was 5.5 ± 1.975 and 5.37 ± 3.404 , respectively ($p=0.882$). Comparison of two groups in terms of frequency of fever, infection, hospitalization, sever neutropenia, neutrophil, and WBC count is shown in Table I. As shown in Table I, a significant reduction was observed in case group in comparison with control group regarding frequency of fever, infection, hospitalization, and neutropenia ($p<0.01$). Moreover, a significant enhancement was seen in case group compared to control group regarding neutrophil and WBC count ($p<0.01$). Table II shows comparison of each group before and after treatment in terms of the frequency of fever, infection, hospitalization, sever neutropenia, neutrophil, and WBC count. As shown in Table II, a significant reduction was observed after intervention regarding the

frequency of fever, infection, hospitalization, and neutropenia ($p < 0.01$). Moreover, a significant enhancement was seen after intervention regarding neutrophil and WBC count ($p < 0.01$). Comparison of patients in second group (end of first and second month), in terms of frequency of fever, infection, hospitalization, sever neutropenia, neutrophil, and WBC count, is shown in Table III. As shown in Table III, there was no significant difference at end of first and

second months in terms of frequency of fever, infection, hospitalization, sever neutropenia, neutrophil, and WBC count ($p > 0.05$).

Comparison of two groups in terms of appetite is shown in Table IV. As demonstrated in Table IV, a significant difference was observed between two groups regarding appetite ($p < 0.05$). In this regard, recovery of appetite was significantly greater in case group than control group.

Table I: Comparison of two groups in terms of frequency of fever, infection, hospitalization, sever neutropenia, neutrophil, and white blood cell (WBC) count

Parameters	Group	Mean \pm SD	P-value
Fever	Case	0.19 \pm 0.107	≤ 0.001
	Control	1.07 \pm 0.206	
Infection	Case	0.81 \pm 0.2	0.002
	Control	1.87 \pm 0.236	
Hospitalization	Case	0.37 \pm 0.178	≤ 0.001
	Control	1.33 \pm 0.187	
Sever Neutropenia	Case	0.11 \pm 0.062	0.001
	Control	0.80 \pm 0.2	
Neutrophil count	Case	2597.5 \pm 243.1	≤ 0.001
	Control	1106.53 \pm 161.6	
WBC count	Case	4062.96 \pm 276.6	0.001
	Control	2566.67 \pm 175.5	

Table II: Comparison of case group before and after treatment in terms of the number of fever, infection, hospitalization, sever neutropenia, neutrophil and WBC count

Parameters	Group	Mean \pm SD	p-value
The number of fever	Before intervention	0.96 \pm 0.136	≤ 0.001
	After intervention	0.19 \pm 0.107	
The number of infection	Before intervention	1.56 \pm 0.209	0.002
	After intervention	0.59 \pm 0.2	
The number of hospitalization	Before intervention	1.15 \pm 0.205	≤ 0.001
	After intervention	0.37 \pm 0.178	
The number of sever Neutropenia	Before intervention	0.78 \pm 0.111	≤ 0.001
	After intervention	0.11 \pm 0.062	
The number of neutrophil count	Before intervention	1609.07 \pm 179.4	≤ 0.001
	After intervention	2597.59 \pm 3243.1	
The number of WBC count	Before intervention	2862.9 \pm 184.1	0.001
	After intervention	4062.96 \pm 276.6	

Table III: Comparison of patients in second group (after two months) in terms of frequency of fever, infection, hospitalization, sever neutropenia, neutrophil, and WBC count

Parameters	Months	Mean \pm SD	p-value
Fever	End of first month	0.93 \pm 0.182	0.48
	End of second month	1.07 \pm 0.206	
Infection	End of first month	1.80 \pm 0.262	0.78
	End of second month	1.87 \pm 0.236	
Hospitalization	End of first month	1.40 \pm 0.235	0.70
	End of second month	1.33 \pm 0.187	
Sever neutropenia	End of first month	0.80 \pm 0.175	1
	End of second month	0.80 \pm 0.2	
Neutrophil count	End of first month	1010.8 \pm 158.6	0.86
	End of second month	1106.53 \pm 161.6	
WBC count	End of first month	2593.33 \pm 181.9	0.9
	End of second month	2566.67 \pm 175.5	

Table IV: Comparison of two groups in terms of appetite

Group	Recovery of appetite	Not recovery of appetite	p-value Chi-Square test
Case	16 (59.3 %)	11 (40.7 %)	0.023
Control	3 (20 %)	12 (80 %)	
Total	19 (45.2 %)	23 (54.8 %)	

Discussion

Fungal infections and febrile neutropenia are the most common causes of mortality in children with ALL (6). Among these infections, bacterial infections are the most common than others. However, other studies reported that fungal infections were seen in 50% of cases of blood malignancies (12,13). In children with ALL receiving treatment, the mortality related to infection decreased using appropriate antibacterial agents (12,13). Increasing incidence of bacterial resistance to antibiotics and the side effects of these drugs were factors in the expansion of research on medicinal plants in recent years. Despite various studies on the different properties of *A. vera*, few studies were performed on the antimicrobial properties of this plant in our country (14). *A. vera* was widely used in herbal medicine as antifungal, antibacterial, antiviral, and anti-inflammatory agents.

In the current study, the use of *A. vera* decreased infection, neutrophil count, and

WBC count. Recently, several studies have been conducted to investigate the role of *A. vera* for treating blood disease and cancer associated with low WBC (10). Olatunya et al., assessed the effect of *A. vera* on HIV infection. In this regard, patients consumed antiretroviral drugs with 30–40 mL of *A. vera* and findings revealed that consumption of *A. vera* may be useful for HIV-infected individuals (15). Ghadiri et al., revealed antibacterial effects of *A. vera* on bacterial pathogens of human and animals (16). In addition, Puch et al., reported that the antibacterial component of *A. vera* was effective against *Escherichia coli*, *Aureus*, *Streptococcus pyogenes*, and *P. aeruginosa* (17). Sadr et al., also demonstrated that the aqueous extract of *A. vera* had an equivalent or better effect than common antibiotics on important infectious bacteria isolated from patients (14). Channa et al., reported that *A. vera* extraction increased the lymphocyte concentration in rabbit. Lymphocytes play a main role in

developing T cell immune and humoral response against foreign antigens, such as viral and bacterial antigens. It seems that acemannan molecule in the aloe gel stimulates the body to produce WBC to fight disease, especially macrophages. These compounds digest unwanted substances, including viruses and bacteria (10).

Other studies revealed that phagocytic activity of reticuloendothelial system was activated in the presence of A. vera (18). Moreover, A. vera increased the cellular and humoral immunity via different mechanisms (19). In addition, improvement of B lymphocyte which is responsible for organization of immunoglobulins M and G has been seen in the presence of A. vera. Furthermore, A. vera can enhance CD8 and CD4 receptor (20). Therefore, increase of lymphocyte may be due to the presence of proteins and glycoproteins with low molecular weight and mitogenic effect, causing proliferation of immune cells (10).

In addition, we observed significant increase in appetite in case group. Mahdavi et al., achieved the same result and reported that A. vera extraction stimulated appetite (21). Chatterjee et al., reported that A. vera was used in treatment of patients with poor appetite (22). Furthermore, fever was decreased in case control compared to control group. Sharma et al., revealed that A. vera reduced fever (23).

Conclusion

According to these findings, A. vera consumption decreased frequency of infection, neutropenia, fever, and hospitalization and increased WBC and neutrophil count. Moreover, appetite was improved in these patients. Therefore, it seems that A. vera can be used for improving quality of life of children with ALL. In addition, there was no significant difference between these parameters at end of first and second months.

Conflict of interest

Authors declared no conflict of interest.

References

1. Sheikhpour R, Hashemi A, Akhondzadeh E, Khanjarpanah Z, Mirakhor M. Evaluation of Immunoglobulin-A Level in Children with Acute Lymphoblastic Leukemia. *Iran J Ped Hematol Oncol* 2017; 7(3): 149-153.
2. Zare-Zardini H, Taheri-Kafrani, Amiri A, Shanbedi M, Sadri Z, Ghanizadeh F, Neamatzadeh H, Sheikhpour R, Keyvani Boroujeni F. Nanotechnology and Pediatric Cancer: Prevention, Diagnosis and Treatment. *Iran J Ped Hematol Oncol* 2015; 15(4): 227-232.
3. Sheikhpour R, Aghaseram M. Diagnosis of acute myeloid and lymphoblastic leukemia using gene selection of microarray data and data mining algorithm. *Sci J Iran Blood Transfus Org* 2016; 12 (4): 347-357.
4. Torkaman A, Moghaddam Charkari N, Aghaeipour M. An approach for leukemia classification based on cooperative game theory. *Anal Cell Pathol* 2011; 34: 235–246.
5. Inaba H, Greaves M, G. Mullighan Ch. Acute lymphoblastic leukaemia. *Lancet* 2013; 381(9881): 1-26
6. Özdemir N, Tüysüz G, Çelik N, Yantri L, Erginöz E, Apak H, Özkan A. Febrile neutropenia in children with acute lymphoblastic leukemia: single center experience. *Turk J Pediatr* 2016;1-10.
7. Hakim H, Flynn PM, Knapp KM, Srivastava DK, Gaur AH. Etiology and clinical course of febrile neutropenia in children with cancer. *J Pediatr Hematol Oncol* 2009; 3: 623-629
8. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. Paediatric Oncology in Developing Countries. SIOP PODC: recommendations for supportive care of children with cancer in a low-income setting. *Pediatr Blood Cancer* 2013; 60: 899-904
9. Sheikhpour R. A Survey on Herbal Medicines for Hypoglycemia in Diabetic Patients. *Iranian J Diab* 2012; 4(1): 40-49
10. Ali Channa A, Hyder Qazi I, Ahmed Soomro S, Hussain Shah A, Gandahi J, Ali Korejo R. Effect of oral supplementation of Aloe vera extract on haematology indices and immune cells of blood in rabbit. *African J Pharmacy and Pharmacology* 2014;1-10.

11. Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. *Aliment Pharmacol Ther* 2004; 19(5):521-527
12. Groll AH, Shah PM, Mentzel C. Trends in postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996; 33: 23-32.
13. Lamagni TY, Eras BG, Shigematzu M, et al. Emerging trends in the epidemiology of invasive mycoses in England and Wales. *Epidemiol Infect* 2001; 126: 397-414.
14. Sadrnia M, Arjomandzadegan M. Comparative study on the effects of Aloe vera extract in clinical strains of *Staphylococcus aureus*, *Klebsiella*, *Staphylococcus epidermidis* and *Escherichia coli* compared to antibiotics of choice. *Arak Med Univ J* 2014; 17(87): 39-46
15. Olatunya OS, Olatunya AM, Anyabolu HC, Adejuyigbe EA, Oyelami OA. Preliminary trial of aloe vera gruel on HIV infection. *J Altern Complement Med* 2012; 18(9):850-853.
16. Gharibi D, Khosravi M, Hosseini Z, Boroun F, Kolsum Barzegar S, Forughi Far A. Antibacterial Effects of Aloe Vera Extracts on some Human and Animal Bacterial Pathogens. *J Med Microbiol Infec Dis* 2015; 1: 6-10.
17. Pugh N, Ross SA, ElSohly MA, Pasco DS. Characterization of Aloeride, a new high molecular weight polysaccharide from Aloe Vera with potent immunostimulatory activity. *J Agri Food Chem* 2001; 49 (2): 1030-1034.
18. Im SA, Oh ST, Song S, Kim MR, Kim DS. Et al. Identification of optimal molecular size of modified Aloe polysaccharides with maximum immunomodulatory activity. *Int. Immunopharmacol* 2005; 5:271-279.
19. Boudreau MD, Beland FA. An evaluation of the biological and toxicological properties of Aloe Barbadensis (Miller), Aloe vera. *J. Environ. Sci. Health* 2006; 24:103-154.
20. Ghasem V, Mehdi T, Amin KM, Reza H. The effect of Aloe vera extract on humoral and cellular immune response in rabbit. *Afr. J. Biotechnol* 2011; 10(26):5225-5228.
21. M. Mahdavi, A. Hajimoradloo and R. Ghorbani. Effect of Aloe vera Extract on Growth Parameters of Common Carp (*Cyprinus carpio*). *WJMS* 2013; 9 (1): 55-60.
22. Chatterjee P. Aloe vera plant: Review with significant pharmacological activities. *Mintage J Phamaceutic Med Sci* 2013; 1-9.
23. Sharma P.A Review on Pharmacological Properties of Aloe vera. *Int J Pharmaceutical Sci Revi Re* 2014; 29(2):31-37