

Impact of garlic tablets on nosocomial infections in hospitalized patients in intensive care unitsHossein Madineh¹, Farrokh Yadollahi², Farshad Yadollahi³, Ebrahim Pouria Mofrad⁴, Majid Kabiri⁵

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Type of article: Original**Abstract**

Background: Nosocomial infections are one of the main causes of mortality and morbidity in hospitals, especially in intensive care units (ICUs).

Objective: The aim of this study was to examine the impact of garlic tablets on nosocomial infections in hospitalized patients in intensive care units.

Methods: This clinical trial was carried out on 94 patients, admitted to the intensive care units in Kashani and Al-Zahra hospitals from January 21, 2014 to December 20, 2014. Firstly, the patients were randomly selected by simple sampling, then they were assigned into case and control groups. The case group administered one 400 mg garlic tablet daily for 6 days and the control group received placebo. During the study, inflammatory blood factors and infection occurrence in the two groups were compared. The Data were analyzed by SPSS software version 22 through descriptive tests such as independent t-test, Chi-square test, ANOVA and exact Fisher test for the analyses of primary and secondary outcomes.

Results: During the study period, 78 cases of intravenous catheter tip were sent to laboratory for culture, of which, 37 cases were in the intervention group and 41 in the control group. Culture results of Catheter tips was positive in 5 cases and all five cases were in the control group. Frequency distribution of catheter tip culture was significantly higher in the control group than that of the intervention group ($p=0.03$).

Conclusion: Based on the results of our study, in people with weakened immune systems and in people with high incidence of opportunistic infections, it is necessary to strengthen their body's immune system stimulants before dealing with these infectious agents, and cause decrease in the diseases insusceptible people. It was suggested that garlic supplementation has shown to be effective in patients admitted to ICU, who are highly susceptible to nosocomial infection, and it can be used for the prevention of septicemia and urinary tract infections. However, further research with larger sample size is needed.

Trial registration: The trial was registered at the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with the Irct ID: IRCT207406156480N6.

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1. Introduction

Nosocomial infection is an important cause of mortality and morbidity in hospitals (1, 2). One of the most common places where these infections occur are intensive care units of hospitals (2-4). Nosocomial infections occur in cases of hospitalization after 48-72 hours of hospital admission (5-8). If infection occurs less than 48 hours after hospitalization, it is likely that the patient was in the incubation stage of the disease during hospital admission. Worldwide, one in four patients hospitalized in ICU are infected and it is estimated that the rate is double in developing countries. Hospital infections are important from several aspects including cause of mortality and illness, increase in the duration of hospitalization, increased costs due to prolonged hospitalization, and diagnostic and treatment procedures of transmission of microorganisms in hospitals. Although one-third of nosocomial infections are preventable, this complication still jeopardizes developing as well as developed countries) 9-13). Pneumonia is the most common followed by urinary tract infection, and sepsis is the most fatal hospital-acquired infection (14). Urinary tract infection occurs mostly during catheterization. Microorganisms can spread in different ways in hospitals. Transmission methods of microorganisms in hospitals include: 1) Transmission by contact (direct contact surfaces of the body and the physical transfer of microorganisms between a susceptible host and an infected or colonized person with microbes; indirect contact of a susceptible host with contaminated equipment, needles, bandages, gloves; and droplet produced by a person during sneezing, coughing and talking, suctioning or bronchoscopy and the contact by the conjunctiva, nasal mucosa); 2) Transmitted through the air (Airborne); 3) Transmitted by contaminated joint food, water, medicines and contaminated equipment; and 4) Transmission by vectors such as mosquitoes, flies and mice that have little significance in the transmission of nosocomial infections (14). Predisposing factors of nosocomial infections include age, systemic disorders, congenital or acquired immune deficiency, defense mucocutaneous, anesthesia and sedation, the use of antibiotic, colonization of flora, urinary tract infections, and latent infections (15, 16). Different types of nosocomial infections include: a) Surgical wound infection; b) Blood infection or sepsis (sepsis); c) Urinary tract infections; d) Pneumonia (respiratory infection). Each of these infections have different symptoms. The common symptoms consist of fever, chills, rapid heart rate, hypotension, dizziness, urine reduction, nausea and vomiting, diarrhea, skin rash, red rash or red spots on the body and joint pain (15, 16). The most common nosocomial infections are respiratory and urinary tract infection (17, 18). There are three potential ways for bacteria to enter the urinary tract and to cause infection, including ascending urinary tract infection and blood and lymph types of infection (19-21). Aerobic bacteria in 87%, fungi in 9% and viruses and parasites in 1% are the causes of hospital infections (22). Garlic has been confirmed to be effective against gram-positive, gram-negative, and acid-fast bacteria including Salmonella, Escherichia coli, Pseudomonas, Proteus, Staphylococcus aureus, Klebsiella, Micrococcus, Bacillus subtilis, Clostridium, Mycobacterium, and Helicobacter. It has been documented that garlic exerts a differential inhibition between beneficial intestinal microflora and potentially harmful enterobacteria. Many fungi are sensitive to garlic, including Candida, Torulopsis, Trichophyton, Cryptococcus, Aspergillus, Trichosporon, and Rhodotorula (23). The exact mechanism of all chemical compounds of garlic has not been identified (23). However, the antibacterial activity of garlic is widely attributed to allicin. Allicin is made up of freshly crushed garlic homogenates. The antimicrobial effect of allicin is mainly related to its chemical reaction with thiol groups of various enzymes influencing the essential metabolism of cysteine proteinase activity involved in the virulence of E. histolytic (24). It is found that allicin has sulfhydryl modifying activity and has capability of inhibiting sulfhydryl enzymes. Cysteine and glutathione counteract the isolation activity of allicin. Garlic extract and allicin have been demonstrated to exert bacteriostatic effects on some vancomycin-resistant enterococci. Garlic extracts have been shown to decrease the oxygen uptake, reduce the growth of the organism, inhibit the synthesis of lipids, proteins, and nucleic acids, and damage membranes (23). Germicidal and disinfectant properties of garlic have long been established (23). Due to the increasing resistance of microorganisms to antimicrobial drugs, as well as the problems developed by the strains in nosocomial infections and people with weak immune systems, the need to pay more attention to new herbal medicines become more significant. With regard to high prevalence of nosocomial infection, particularly in ICU, as well as excessive use of antibiotics in this unit as prophylaxis, and the development of drug resistance these days, finding a way to limit antibiotic consumption can be very beneficial. Use of garlic as a herbal medicine, and its antibiotic use, can be effective in reducing infections and decreasing antibiotic resistance in the community. Thus, the aim of this study was to examine the impact of garlic tablets on nosocomial infections in hospitalized patients in ICU.

2. Material and Methods

2.1. Trial design

This double blinded clinical trial study was carried out in patients admitted to the general adult intensive care unit of Kashani and Al-Zahra hospitals in Shahrekord from January 21, 2014 to December 20, 2014. In this study, 100 eligible patients were randomly divided into two groups of 50.

2.2. Participants

Six patients (3 from intervention group and 3 from control group) left the study, and finally, data of 47 patients in each group were studied. Then the eligible patients were selected based on the inclusion and exclusion criteria. Informed consent form was signed by the patients' relatives (as the patients were unconscious).

2.3. Selection criteria

Inclusion criteria: patients admitted to the general adult intensive care unit, age ranged between 15 and 55 years, consented to participate in the study. Patients who were excluded from the study were those with systemic disease or immunocompromised patients with AIDS or leukemia or decreased white blood cells or those suffering from diabetes together with those who underwent surgery with high risk of infection such as purulent perforated appendicitis or bowel surgery, patients with severe injury having high risk of suffering sepsis (e.g. burns more than 9%, open fractures). Also, patients who had sepsis on admission or infectious sores or fever greater than 38.3, patients who had bleeding risk, patients with more than 10 days hospital stay and those who take corticosteroids at high dose (60 mg daily) were also excluded from study.

2.4. Interventions

The first group was daily gaviged one garlic tablet (Garlic tablets 400 mg, Gol Darou Company) in powder form for 6 days. The dosage was decided based on previous similar studies (24, 25). Gavage was carried out through NGT (Gastric intubation via the nasal passage (i.e., the nasogastric route) and the correct location of the tube in the stomach was determined. To do this, stomach contents were aspirated and the sound of the air entrance to the stomach was heard. The garlic tablet was powdered and was dissolved by distilled water and gaviged through a syringe. Then the NGT route was washed with 30cc of water. The pipes were clamped intermittently during every second gavage. The tablet was administered once daily in the morning. Both the intervention and control group received routine ICU surveillance. The control group was administered starch tablet as placebo. Having switched the venous catheter tip every 72 hours, it was sent to the laboratory in a sterile manner for culture; culture and antibiotic sensitivity tests were performed. Based on the indication of urinary catheters switching, whenever urinary catheter was, its tip was sent to the laboratory for culture and antibiotic sensitivity test. Additionally, the patients' blood sample was taken every 72 hours to determine total blood count and blood sugar, and urine samples were used to determine the urinary white blood cells. Both blood and urine samples were collected and sent to the laboratory. Body temperature was measured by a thermometer for up to 6 days (first day to sixth day) every six hours. Urine catheter was switched and sent for culture for up to 6 days (first day to sixth day). White blood cells urine and urine culture were measured up to 6 days (first day to sixth day) the temperature of the patients' bodies were recorded, signifying the incidence of infection. Moreover, full blood count, fasting blood sugar and patient core temperature were sent to the patient, based on their test, and the patient's thermometer chart was recorded in the patient questionnaire at the end of the interval by the researcher. ESR and CRP at baseline and every 48 hours were measured for up to 6 days. The findings and culture results and other information were recorded in a researcher-designed checklist. Patients in ICU were taken care of, by ICU nurses. The nurses were responsible for assigning the garlic tablet and placebo and to take samples. The laboratory pathologists of Al-Zahra and Kashani hospitals tested the samples.

2.5. Outcomes

The primary outcomes of our analyses were the blood sugar, blood cell count and body temperature in the two groups. Also, the secondary outcomes from the analyses were urinary white blood cells, INR, PT and PTT and the patients' satisfaction with the garlic tablet.

2.6. Sample size

Sample size was determined using formula $n = 2 (Z_{1-\alpha/2} + Z_{1-\beta})^2 P(1-P)/d^2$; where: $\alpha=0.05$, $\beta=0.2$, $P=0.5$, $Z_{1-\alpha/2}=1.96$, $Z_{1-\beta}=0.84$, and $d=0.3$.

2.7. Randomization and blinding

Neither the nurses nor the physician were informed of the Drug Code. Randomization was done using the coded papers. The patients in each group were matched in terms of age, sex, and antibiotic intake. Both the garlic and starch tablets were of the same size and color, and had an identical packaging.

2.8. Statistical methods

The Data were analyzed by IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) through descriptive tests such as independent t-test, Chi-square test, ANOVA and exact Fisher test for the analyses of primary and secondary outcomes.

2.9. Research ethics

The proposal for this thesis research was presented to the Ethics Committee of Shahrekord University of Medical Sciences after its scientific approval. The Ethics Committee approved the study with the ethical code 93319. This study was also registered in the Iranian Registry of Clinical Trials (irct.ir) with the ID: IRCT207406156480N6. The authors confirm that all ongoing and related trials for this drug/intervention are registered. Indeed, in this study, for ethical considerations, the participants were informed about the objective and nature of the study, and each participant entered into the study voluntarily and provided with written consent in her native language (Persian) prior to the study. Each patient was free to leave the study for any reason whenever they wanted. Also, we were committed to keeping all of the participants' information confidential. This study with grant no 1143 was conducted in Kashani and Al-Zahra hospitals.

3. Results

In this study, 94 patients who were admitted to the intensive care unit were distributed into either the case group (receiving garlic tablets) or the control group. The mean age of patients in the intervention group and control were 43.58 ± 16.84 and 38.42 ± 12.54 years respectively and there was no significant difference between mean age of the two groups ($p=0.11$). There were 32 and 30 males (74.4% vs. 69.8%) in intervention and control groups, respectively, and no significant difference was observed between the two groups ($p=0.63$). Table 1 showed the demographic information of both groups. In Table 2, mean and standard deviation of body temperature at the end of the first, third and sixth days in the two groups were tabulated. Mean of body temperature at the second and fourth days were significantly higher in the control group ($p<0.05$), but on other days, no significant difference was observed ($p>0.05$). It was shown that there was a significant difference between body temperature changes between the two groups ($p=0.007$). To find the mean of body temperature, the data of three days were added and then divided into the number. The mean and standard deviation of PT, PTT, INR, WBC, RBC, and FBS at the end of the first, third and sixth days in the two groups was tabulated in Table 3. None of the variables were shown to be significant. During the study, 78 samples of venous catheter tip culture were sent to the laboratory, of which 37 cases related to the intervention group and 41 cases related to the control group (as the culture result of other samples were contaminated, only venous catheter tip cultures of 78 samples were tested). The culture result of venous catheter tip was positive for 5 cases, of which, all were related to the control group and no cases of positive culture result was observed in the intervention group. It also showed that the frequency distribution of catheter tip culture was significantly higher in the control group ($p=0.03$). During the study period, urine tests were taken from 36 patients in the intervention group and from 32 patients in the control group. The mean of urine white blood cells in the intervention and control groups were 4.41 ± 4.04 and 4.48 ± 4.1 , respectively. No significant difference was observed between the two groups ($p=0.48$). During the study, a culture test was taken from 35 patients in the intervention group and 30 patients from the control group. The culture result was positive for two patients in the intervention group and six patients in the control groups. With regard to the positivity of the culture result, the difference between the two groups was not statistically significant ($p=0.13$). One patient in the intervention group died during the study period (cause of death was reported to be due to trauma within a few days of ICU admission, not related to the intervention), but no death occurred in the control group (2.3% vs. 0%) and there was no significant difference between the two groups ($p=0.99$) (Table 4).

Table 1. Demographic information of intervention and control group

Group	Sex; n (%)	Age (year); Mean \pm SD
Intervention	Male	32 (74.4)
	Female	15 (35.6)
Control	Male	30 (69.8)
	Female	17 (30.3)

Table 2. Mean and standard deviation of BT (Body temperature) of patients at the end of the first, third and sixth days in the two groups.

Day	Group		
	Control (°C)	Intervention (°C)	p-value
At the baseline	37.2±0.35	37.16±0.53	0.71
First	37.39±0.56	37.2±0.52	0.13
Second	37.51±0.56	37.25±0.56	0.03
Third	37.41±0.71	37.28±0.5	0.34
Fourth	37.47±0.64	37.15±0.54	0.09
Fifth	37.47±0.52	37.26±0.62	0.34
Sixth	37.43±0.59	37.22±0.51	0.1

Table 3. Mean and standard deviation of, PT, PTT, INR, WBC, RBC, and FBS at the end of the first, third and sixth in the two groups

Variable and day		Group		
		Intervention	Control	p-value
PT	First	14.88±2.47	14.31±4.3	0.46
	Third	14.84±3.39	15.85±6.54	0.38
	Sixth	13.49±2.8	14.01±4.47	0.54
PTT	First	36.67±10.79	33.56±8.05	0.14
	Third	34.14±6.51	36.13±9.5	0.27
	Sixth	36.56±12.52	34.82±7.35	0.45
INR	First	1.78±1.5	1.37±0.31	0.09
	Third	1.49±0.49	1.58±0.76	0.55
	Sixth	1.43±0.22	1.93±0.33	0.37
WBC	First	11.12±5.1	10.76±4.78	0.74
	Third	10.4±4.5	11.33±5.51	0.39
	Sixth	10.12±35.58	10.06±52.36	0.91
RBC	First	4.03±1.49	3.95±0.7	0.77
	Third	3.86±2.4	3.69±0.65	0.67
	Sixth	3.62±0.64	3.76±0.64	0.33
FBS	First	146.67±64.86	137.77±87.82	0.59
	Third	131.4±43.1	120.33±27.25	0.16
	Sixth	134.07±46.29	121.37±40.12	0.19

Table 4. Venous catheter tip culture results and urine culture results in both intervention and control groups

Variable		Intervention		Control		Total	
		%	n	%	n	%	n
Venous catheter tip culture result	Negative	100	37	87.8	36	93.6	73
	Positive	0	0	12.2	5	6.4	5
	Total	100	37	100	41	100	78
Urine culture result	Negative	94.3	33	80	24	87.7	57
	Positive	5.7	2	20	6	12.3	8
	Total	100	35	100	30	100	65

4. Discussion

The main aim of this study was to determine the effect of garlic tablet on culture results of samples obtained from peripheral central urinary catheters, and inflammatory factors in ICU patients. In this study, two groups of 47 patients admitted to the ICU were studied for six days. Based on the results of our study, no significant difference was observed between the intervention and control groups during the 6 days of study period with regard to inflammatory factors, the level of white blood cells, blood sugar levels and red and white blood SOFA index. Therefore, it can be concluded that taking garlic tablets had no significant effect on the aforementioned parameters, but based on the result obtained, the mean of body temperature that is an indicator of infection occurrence had a significant difference between the two groups during the study, and the patients receiving garlic tablet had lower

body temperature. Moreover, there were no cases of venous catheter infection in the group receiving garlic tablet while 12.2% of patients in the control group suffered from venous catheter infection. Cases of urinary infection were significantly higher in the control group but the difference was not statistically significant. In a study by Tsao et al. in 2001, in vitro antibacterial activities of garlic oil and four diallyl sulphides naturally occurring in this oil were studied against *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, and it was found that garlic oil, through synergic or additive effects, could be potentially used to prevent or treat antibiotic-resistant bacteria-caused nosocomial infections (26). In a study by Dikasso et al, antibacterial effect of garlic prepared by agar technique was examined against some causes of pneumonia and it was confirmed that streptococcus pneumonia was completely removed through 8.7 mgr/ml of this solution, and clinical samples of *Klebsiella pneumonia* were inhibited by 38.24 mgr / ml of this solution. The study showed that streptococcus compared with the *Klebsiella* was more sensitive to garlic and it was demonstrated that garlic can act effectively on microorganisms (27). In a research by Dankert et al, the inhibitory effect of garlic, onion and shallot extracts was examined by agar diffusion test on the growth of a number of bacteria and yeasts, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*. According to the study, all organisms were inhibited by garlic extract. High concentrations of garlic extract possess bactericidal effect on *Pseudomonas aeruginosa* (28). In a study by Josling and his colleagues, 146 individuals were randomly selected into two groups receiving placebo and garlic allicin. Both groups were evaluated at 12 weeks and it was observed that the volunteers in the active group not only had less number of colds but also recovered quickly in the event of infection. Finally, the compound prepared from garlic can severely reduce the number of virus colds (29). In a study by Elnima, comparing the effects of garlic (*Alliumsativum*) and onion (*Allium cepa*) extracts on the number of positive and Gram-negative fungus, it was shown that garlic extract has more bactericidal and bacteriostatic activities than onion extract. Furthermore, the effect of garlic extract on normal flora of the mouth of volunteers were investigated. Mouthwashes containing 70% of garlic extract in Ringer's solution showed a significant decrease in all bacteria in the mouth (30). In another study, inhibitory effects of extracts of garlic and onions on the isolated bacteria, including four Gram-negative bacteria, were studied and the results showed that extracts of garlic and onion can compete with Gram-positive bacteria and with only one Gram-negative isolated bacteria (*Klebsiella pneumonia*). Inhibitory effects of allicin on nine different species of fungi such as *Microsporium*, *Canis M. gypseum*, and *Trichophyton simii* were also observed while growing mushrooms such as *Chrysosporium*, *Trichophyton Mentagrophytes* PPM *Queenslandicum* were inhibited by the extract (30). In a study by Alice, properties of several antibiotics, including streptomycin sulfate 90%, tetracycline hydrochloride (10%), and esterptociclin with garlic and onion extracts were compared. It was found that inhibitory effects of garlic extract on enzymes of the Patton microorganisms wall, particularly (PG) and (PL) was similar to antibiotics (31). The study by Fang et al., indicated that in comparison with the *Klebsiella* bacteria, pneumonia was more sensitive to garlic, and indicated that garlic can act as an effective substance on microorganisms (32). Similar to all herbal-based medicine, garlic extract was used in traditional medicine in vivo to kill bacteria, fungi and viruses. The effects of garlic extract on Staph have been conducted in in vivo studies on laboratory animals. Aureus methicillin-resistant germs or on Cytomegalic viruses have also been approved (32, 33). Many beneficial effects following the use of garlic diet on patients with a weakened immune system were achieved. Fibrinolytic activity of garlic was shown in platelet aggregation and it was confirmed that, what has traditionally been used for such treatments, still has useful effects on treatment of many diseases (34). It was stated that the effects of garlic on different microorganisms were different from each other, so that even though the same method was used, the effect of extract on different bacteria will not be identical. For example, in the study by Arora et al in 1999, *Staphylococcus epidermidis* bacterium was killed during one hour, but *Salmonella typhi* was killed within 3 hours of exposure to garlic extract (35). Many studies have shown that a garlic compound enhances the phagocytic effect of immune cells (36). So, reinforcing effect of garlic and allicin is more evident because they strengthen phagocytic activity of macrophages and secrete factors. Based on the results of this study, it can be concluded that the garlic tablet is an acceptable compound in inhibition of bacteria growth, especially isolated pathogens of hospital infections.

5. Limitations and suggestions of study

Based on the fact that this study was carried out on patients hospitalized in ICU, the researchers of this study encountered low sample size, which was our limitation. There are some suggestions related to this study: 1) regarding microbicidal property of garlic, it is recommended that similar research in other wards of hospitals is done; 2) It is suggested that the findings of this study are offered to the physicians of different wards of ICU; 3) Garlic tablet consumption is considered as a preventive substance against nosocomial infections; 4) This research is recommended to be repeated in larger sample size; and 5) It is suggested that people's awareness be increased regarding microbicidal property of garlic through mass media.

6. Conclusions

Based on the results of our study, in people with weakened immune systems and in people with high incidence of opportunistic infections, it is necessary to strengthen their body's immune system stimulants before dealing with these infectious agents, and to cause decrease in the diseases in the susceptible people. It was suggested that garlic supplementation has shown to be effective in patients admitted to intensive care units and those who are highly susceptible to nosocomial infection, and it can be used for the prevention of septicemia and urinary tract infections. Further research with larger sample size is needed.

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Trial registration:

The trial was registered at the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with the Irct ID: IRCT207406156480N6.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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