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The Effects of Quercetin Topical Cream on Phlebitis Caused by Peripheral Intravenous Catheters: A Randomized Controlled Trial

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Abstract

Background: Phlebitis is among the most common complications of intravenous therapy. It significantly correlates with the length of hospital stay and mortality rate.

Objectives: This study sought to examine the effects of quercetin topical cream on phlebitis caused by peripheral intravenous catheters.

Methods: This single-blind randomized controlled trial was done in 2015 on 66 patients hospitalized at the internal medicine ward of Valiasr (PBUH) hospital, Birjand, Iran. The patients were conveniently recruited and randomly allocated to a control and an experimental group. The data collection tool was a five-point phlebitis assessment scale. As soon as the symptoms of phlebitis were observed, the related catheter was removed and the catheter insertion site was treated every twelve hours for 72 hours with either 2% quercetin cream (the experimental group) or a eucerin-based cream (the control group). Friedman, Wilcoxon and Mann-Whitney U tests were run using the SPSS software for data analysis (v. 14.0).

Results: There was no significant difference between the groups regarding patients' age ($P = 0.068$) and gender ($P = 0.69$). No significant changes were observed in the severity of phlebitis in the control group during the 72-hour course of the study. However, in the quercetin group, the severity of phlebitis decreased significantly after twelve hours from the beginning of the intervention and the trend of its variations was downward ($P < 0.001$). Consequently, after 72 hours (or six episodes of quercetin cream use), 90% of all phlebitis cases achieved complete recovery without any side effect.

Conclusions: 2% Quercetin cream could be effective in treating phlebitis caused by intravenous catheters and can be used as a useful and safe treatment modality for phlebitis management. The positive effects of quercetin on phlebitis appear very soon after its use.

Keywords: Phlebitis, Quercetin, Intravenous Catheter, and Intravenous Fluid Therapy

1. Background

Alongside rapid medical advances, Intravenous (IV) therapy has turned into an essential part of patient care. Intravenous therapy includes administrating substances directly into the veins for electrolyte deficit management, medication therapy, blood transfusion, hemodynamic monitoring and fluid supplementation (1). Compared with the other routes, IV therapy is the fastest route for delivering fluids and medications to different parts of the body.

Intravenous catheters are the most commonly used medical devices for hospitalized patients (2). Studies showed that around 80% of patients receive IV therapy during the course of their hospitalization. This means that 180 million patients are catheterized each year by using 500 million catheters (3). It is estimated that about 200 million IV devices are used in the United States each year. Besides, the use of IV catheters in Spain increased from 28% in 1990 to 44% in 1999 (4).

Although IV therapy saves many lives, it is an invasive procedure and is associated with different complications. A large group of patients, who receive IV therapy are at risk of its complications, chiefly phlebitis (5). Phlebitis is the inflammation of the intima layer of the veins and is characterized by local pain, redness, edema and palpable thrombosis (6). Based on its etiology, phlebitis can be categorized into three main groups of chemical, mechanical and infectious. Factors associated with mechanical phlebitis include thick and tall catheters, catheter inser-

tion site, number of catheterizations, length of catheterization, infusion rate, dressing used to fix catheters and infusion set replacement schedule. On the other hand, chemical phlebitis is caused by the reaction of the intima with infused medications or solutions, particularly with solutions of high acidity or osmolarity such as hypertonic fluids, amino acids, some antibiotics, and blood products. Infectious phlebitis usually occurs due to the transmission of infecting pathogens from other parts of the body or from the catheter tip to the catheterization site (7).

As a multifactorial condition, phlebitis is caused by three main factors including patient-, catheter-, and catheterization-related factors. Accordingly, patients with diabetes mellitus or obesity, patients receiving immunosuppressive agents, and very young or very old patients are more susceptible to phlebitis (8). Moreover, femininity, fragility of peripheral veins, venipuncture in lower extremities, and affliction by underlying conditions also increase the risk of phlebitis (9). Studies showed that 20% - 70% of patients receiving IV injections are very likely to develop phlebitis. In China, 80% of patients receiving IV injections experience phlebitis (10). Moreover, cephalosporin injection can enhance the risk of phlebitis so much so that 30% - 50% of patients receiving cephalosporin were reported to have phlebitis (11). Total parenteral nutrition is also known to be among the most common causes of phlebitis (12). The prevalence of phlebitis in our country, Iran, is higher than other countries. The mean durability rate for IV catheters in other areas of the world is two to four days while in hospitals located in Tehran, Iran, most cases of phlebitis occur only one day after catheter insertion (13).

Phlebitis is not only life-threatening and can cause clot formation, thrombophlebitis and emboli, but also can decrease the longevity of IV catheters. Therefore, one of the major reasons behind early removal of peripheral IV catheter is phlebitis. Besides, it can increase healthcare costs, waste nurses' time, and cause problems such as infections, discomfort, early catheter removal and re-catheterization. Frequent re-catheterizations, in turn, limit the number of suitable catheterization sites, postpone IV drug administration, and extend hospital stay (14).

Due to its high prevalence and life-threatening complications, phlebitis has always been among the main concerns of healthcare providers, particularly nurses. Nurses have the main responsibilities for assessing peripheral IV catheters for probable complications (such as phlebitis) and taking immediate measures for preventing and managing them (15). The results of several randomized controlled trials showed that using filters, hydrocortisone, heparin, topical corticosteroids, transdermal glyceryl trinitrate, or non-steroid anti-inflammatory topical gels at venipuncture site can reduce the rate of catheter-induced phlebitis (2, 14). However, none of these modalities have been publicly accepted due to concerns over their cost-effectiveness and safety. Accordingly, simpler, safer and more cost-effective modalities are needed (16).

Alternative anti-inflammatory therapies such as medicinal plants have received considerable attention during the recent years. Medicinal plants are natural and have fewer side effects and thus, they can be good substitutes for chemical agents that have low effectiveness and cause significant complications (17). One of the natural substances, which have antibacterial, anti-inflammatory and clogging effects, is quercetin. Quercetin is a natural flavone and is found in fruits, vegetables, tea, and most dietary supplements with many beneficial effects on health (18). Quercetin is an antiulcer and peroxidation-reducing agent. It has a wide range of biological anticancer, anti-inflammatory and antiviral functions. Besides, it inhibits lipid peroxidation, platelet aggregation and capillary permeability (19). In vivo studies have shown the strong antioxidant effects of quercetin. The anti-inflammatory effects of quercetin are due to its inhibitory effects on cytokine release. Moreover, quercetin has a significant role in sustaining Th1/Th2 balance in response to inflammatory reactions of human dermal fibroblast. It also induces the expression and production of IL-4 and IFN-g in peripheral blood mononuclear cells (20).

No studies have been performed so far on the effects of quercetin on catheter-induced phlebitis. However, the findings of previous studies denote that it may be potentially effective in reducing the severity of phlebitis.

2. Objectives

The present study sought to examine the effect of quercetin topical cream on phlebitis caused by peripheral IV catheters.

3. Methods

This single-blind randomized controlled trial was done in 2015 on 66 patients hospitalized at the internal medicine ward of Valiasr (PBUH) hospital, Birjand, Iran. The ethics committee of Birjand University of Medical Sciences, Birjand, Iran, approved the study (approval code: IR.BUMS.1394.28). The study was registered in the Iranian registry of clinical trials with registry code of IRCT2015061422738N1.

After obtaining necessary permissions from the ethics committee of Birjand University of Medical Sciences, we referred to the study setting, recruited eligible patients through convenient sampling, and allocated them to an

experimental and a control group (33 patients in each group) via systematic random allocation technique. The sample size was calculated based on the findings reported by Haji-Hossaini et al. in 2007, i.e. a S1 of 0.65, a S2 of 0.01, and a d of 0.52 as well as a confidence interval of 0.95 (21). Sampling was done in three consecutive months during autumn 2015. The selection criteria included having an IV catheter in upper extremities, undergoing venipuncture under sterile conditions, being hospitalized in internal medicine ward for at least 72 hours, age of 18 to 60 years, having no sensitivity to medications or adhesive tapes, receiving no blood products, having a systolic blood pressure of 90 - 180 mmHg, lack of diabetes mellitus or skin lesions at catheter insertion site, not being pregnant or breastfeeding, having at least one of the phlebitis-related symptom (i.e. pain, redness, or inflammation), using no medication or herbal oil for phlebitis, and no sensitivity to quercetin. The patients were excluded if they used contraceptive agents, had known coagulopathies (such as anticardiolipin antibody, antiphospholipid antibody, or vitamin C deficiency), were reluctant to remain in the study, died during the study, or if their hospital-stay was less than three days.

Two instruments were used for data collection. The first one contained items on the patients' demographic characteristics, catheter insertion site, and the type of fluid infused through the catheter. The second instrument was the five-point phlebitis assessment scale developed in 2014 by Akbari et al. (22). The points on the scale were,

- No phlebitis: There is no phlebitis-related symptom (including pain, redness, edema, and tenderness);

- First-degree phlebitis: There is one phlebitis-related symptom, either pain or redness;

- Second-degree phlebitis: There is pain, redness, or edema at catheter insertion site; the borders of the vein are detectable;

- Third-degree phlebitis: There is pain, redness, or edema at catheter insertion site; the borders of the vein are detectable; the vein is not cord-like;

- Fourth-degree phlebitis: There is pain, redness, or edema at catheter insertion site; the borders of the vein are detectable; the vein is cord-like.

All patients with an IV catheter in place were approached. As soon as the symptoms of phlebitis were identified, the catheter was removed and a new venipuncture was made at another site. Before the intervention, the severity of phlebitis was assessed using the five-point scale and then, patients with first-, second-, and third-degree phlebitis were randomly allocated to the control and the quercetin groups. Accordingly, the first and the second eligible patients were randomly allocated to the first and the second groups. Subsequent patients were alternately allocated to the groups.

Hand-made 2% quercetin cream was used in the study. The cream was made under hygienic conditions in an experimental medicine laboratory by using quercetin (Merck Company, Germany) and eucerin (Emad Darman Company, Iran). Eucerin is water-absorbent and hence, helps stabilize quercetin. A fifteen-gram tube of quercetin cream was prepared for each patient through adding four grams of water and ten grams of eucerin to one gram of quercetin. Patients in the control group were treated with a cream, which only contained water and eucerin. The amount of eucerin in tubes used for the patients in the control group was the same as the amount used for their counterparts in the experimental group. Moreover, the general appearance of the tubes was similar in both groups. Topical creams were applied on the inflamed venipuncture site for 72 hours and on a surface area of 3×4. Then, the site was covered with a sterile dressing. Every twelve hours, the dressing was removed, the site was assessed regarding phlebitis-related symptoms (including warmness, redness, pain, tenderness, or edema), phlebitis severity was measured, and the site was cleaned. Then, cream and dressing were applied again to the site. All these steps were taken for patients in both groups.

The covers of the quercetin and placebo tubes were the same. They had been labeled as A and B and thus, the patients were blind to their content. The intervention and the assessments were performed by the one person. Furthermore, all patients in both groups were provided with training regarding the standard conditions of the study. In addition, before the intervention, they were assessed for any sensitivity to the preparations. Accordingly, small amount of each preparation was applied to a 2×2 cm^2 area of their arms and 20 minutes later, the site was assessed for sensitivity (23). Patients, who showed sensitivity, were not included in the study.

The SPSS software (v. 14.0) was used for data analysis. Primarily, the normal distribution of the study variables was assessed with the Kolmogorov-Smirnov test. The measures of descriptive statistics (such as mean, standard deviation, and absolute and relative frequencies) were used for data description. The independent-sample t and the Chi-square tests were also used to compare the groups regarding the patients' age and gender. Moreover, Friedman and Wilcoxon tests were run to assess within-group variations while the Mann-Whitney U test was run to make between-group comparisons. The level of significance was set at less than 0.05.

4. Results

In total, 66 patients participated in this study. Most of the patients in the quercetin and the control groups were female (54.2% vs. 57.6%). The means of the patients' age in these groups were 50.54 ± 1.21 and 54.78 ± 8.70, respectively. There was no significant difference between the groups regarding the patients' age (P = 0.068) and gender (P = 0.69). The most common catheterization site in the quercetin and the control groups were, respectively, the forearm (66.7%) and the antecubital fossa (45.5%) while the least common site in both groups was the wrist (Table 1). Moreover, the most commonly infused IV solution in both groups was the 1/3 -2/3 solution (47%).

Before the study intervention, the groups were matched regarding the degree of phlebitis. In other words, the rates of first-, second-, and third-degree phlebitis in both groups were 27.3%, 63.6% and 9.1%, respectively. The Fisher's exact test revealed no significant difference between the groups regarding phlebitis severity (P = 1.0). Before the intervention, the mean phlebitis severity in both groups was 1.81 ± 0.58. The groups were compared with each other regarding the mean of phlebitis severity at different measurement time points (Table 2). All posttest mean values of phlebitis severity in the quercetin group was significantly less than the control group (P < 0.001).

The results of the Friedman test for within-subject comparisons illustrated that in both groups, there was a significant difference among different time points regarding the mean of phlebitis severity (P < 0.001). Consequently, the Wilcoxon test was run for pretest-posttest pairwise comparisons in each group (Table 3). This test showed that in the control group, the pretest mean value of phlebitis severity was not significantly different from any of the phlebitis severity mean values related to different posttest measurement time points including 12, 24, 36, 48, 60 and 72 hours after the intervention onset (P > 0.05). However, in the quercetin group, all of these differences were statistically significant (P < 0.05). It is important to mention that the application of the creams caused no side effects for the participants. Moreover, none of the study participants died, withdrew from the study, or was discharged from the study setting.

5. Discussion

This study was performed to examine the effects of quercetin topical cream on phlebitis caused by peripheral IV catheters among 66 patients recruited from Valiasr (PBUH) teaching hospital, Birjand, Iran. Accordingly, the severity of catheter-induced phlebitis was determined and catheter insertion sites were treated every twelve hours for 72 hours with either 2% quercetin cream (the experimental group) or eucerin-based cream (the control group). The variations of phlebitis severity were monitored in both groups.

The results of the study illustrated that in the control group, the severity of phlebitis did not change significantly during the 72-hour course of the study intervention. However, in the quercetin group, it decreased significantly after twelve hours from the beginning of the intervention and the trend of its variation during the intervention was downward. Consequently, after 72 hours of using quercetin cream, 90% of all phlebitis cases in the quercetin group achieved complete recovery. These findings indicated that quercetin cream significantly reduced phlebitis severity among the study participants (P < 0.001).

In our literature review, we could not find any study on the effects of quercetin on phlebitis. However, in agreement with our findings, previous studies have shown that quercetin can reduce the amount of inflammation mediators. For instance, the results of a study performed in Korea by Jung et al. (2010) revealed that quercetin and tannic acid alleviated the symptoms of atopic dermatitis and reduced the expression of Tumor Necrosis Factor (TNF)-a and the polarization of Th2 in mice (20). The results of another study performed in Egypt by El Goweini and El Din (2005) also illustrated the positive effects of quercetin on skin wounds. They inflicted minor wounds on the ears of rabbits and applied quercetin cream on the wounds for eight weeks. After this eight-week intervention, 40% of the rabbits achieved complete recovery. Moreover, the blood levels of histamine and hydroxyl proline reduced significantly after their intervention (24). Koohpayma et al. (2005) also investigated the effects of quercetin on wound healing among dexamethasone-treated rats. After inflicting skin wounds around the spine, they treated the rats with dexamethasone, quercetin, or both for 21 days. Wound healing was assessed through measuring the percentage of healing, the length of the wounds, the duration of wound healing, and the tensile strength of the wounds. Their findings showed that the rate of wound healing was higher among dexamethasone-treated rats that had received quercetin. Besides, the duration of wound healing among these rats was significantly shorter than rats, which had been treated solely with dexamethasone (25). Zheng et al. (2012) also performed a review study to determine the effectiveness of Aloe vera in the prevention of phlebitis. They found that topical use of fresh Aloe vera, either singularly or in combination with other products, can be effective in preventing and treating phlebitis induced by IV therapy (1).

To the best of our knowledge, the effects of quercetin on phlebitis have not been evaluated among human subjects. In other words, studies on the effectiveness of

Table 1. The Frequency Distribution of Catheter Insertion Sites in Both Groups

Catheter Insertion Site	Group			
	Control (n = 33)		Quercetin (n = 33)	
	N	%	N	%
Antecubital fossa	15	45.5	5	15.2
Forearm	12	36.3	22	66.7
Wrist	3	*	0	0
Dorsal surface of the hand	3	9.1	6	18.1

Table 2. Comparison of the Study Groups Regarding Phlebitis Severity at Different Time Points

Time	Group		
	Quercetin (n = 33) Mean ± SD	Control (n = 33) Mean ± SD	The results of the Mann-Whitney U test
Before the intervention	1.81 ± 0.58	1.81 ± 0.58	P = 1
12 hours after the intervention	1 ± 0.75	1.66 ± 0.47	P < 0.001
24 hours after the intervention	0.69 ± 0.72	1.60 ± 0.49	P < 0.001
36 hours after the intervention	0.93 ± 1.78	1.51 ± 0.66	P < 0.001
48 hours after the intervention	0.30 ± 0.63	1.51 ± 0.66	P < 0.001
60 hours after the intervention	0.21 ± 0.48	1.48 ± 0.71	P < 0.001
72 hours after the intervention	0.15 ± 0.44	1.48 ± 0.71	P < 0.001
The results of the Friedman test	P < 0.001	P = 0.001	-

Table 3. Comparison of Different Measurement Time Points in Both Study Groups by Using the Wilcoxon Test

Time	Group	
	Quercetin (n = 33)	Control (n = 33)
Before-12 hours after	P < 0.001	P = 0.059
Before-24 hours after	P < 0.001	P = 0.059
Before-36 hours after	P < 0.001	P = 0.063
Before-48 hours after	P < 0.001	P = 0.063
Before-60 hours after	P < 0.001	P = 0.059
Before-72 hours after	P < 0.001	P = 0.059

quercetin are limited to animal experiments. As strong antioxidants that scavenge free radicals, flavonoids like quercetin can be suitable agents for promoting wound healing. Quercetin is a biologically-active compound that has been known to have protective effects on skin tissue cells against oxidative injuries. However, in order to understand its mechanism of action in accelerating phlebitis healing, the markers of oxidative stress need to be measured in the presence of quercetin in future studies.

5.1. Conclusion

The findings of the present study indicated that topical use of 2% quercetin cream is a simple, effective, cost-effective, and feasible method for treating catheter-induced phlebitis. Accordingly, it can be used as a treatment modality.

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