Review Article

Meta-analysis of Aloe vera for the prevention and treatment of chemotherapy-induced phlebitis

Yulu Gao1*, Ting Jiang4*, Shencong Mei2*, Shaoli Zhang2, Changtai Zhu2, Yongning Sun3

1Department of Laboratory Medicine, Kunshan Hospital Affiliated to Nanjing University of Traditional Chinese Medicine, Kunshan, China; 2Department of Outpatient, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai, China; 3Department of Traditional Chinese Medicine, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai, China; 4Department of Orthopedics, The Third Affiliated Hospital, Anhui Medical University, Hefei, China.

*Equal contributors.

Received January 4, 2016; Accepted April 1, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: As a common side effect among cancer patients, chemotherapy-induced phlebitis (CIP) not only causes new health hazards to the patients, but also affects the smooth implementation of chemotherapy. In recent years, Aloe vera has been frequently used for the prevention and treatment of CIP in clinical practice. In this study, our aim was to evaluate the clinical value of Aloe vera for the prevention and treatment of CIP. The databases: MEDLINE, EMBASE, the Chinese Biomedical Literature Database (CBM), the China National Knowledge Infrastructure (CNKI), the Chinese Scientific Journals Full-text Database (VIP), and the Wanfang database were searched. Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), a systematic review and meta-analysis was performed using Review Management 5.0 software. Ten clinical trials related to the prevention of CIP and six trials about the treatment of CIP, involving a total of 4530 patients, were included in this study. Meta-analysis showed that Aloe vera was effective for the prevention of chemotherapy-induced phlebitis. The pooled OR in the Aloe vera external application treatment group was 0.13 (95% CI: 0.08-0.20, \(P < 0.001\)). Further subgroup analysis showed that the OR values in the Aloe vera treatment group for 1st, 2nd, and 3rd degree phlebitis were 0.53 (95% CI: 0.21-1.33, \(P > 0.05\)), 0.10 (95% CI: 0.07-0.14, \(P < 0.001\)) and 0.10 (95% CI: 0.03-0.34, \(P < 0.001\), respectively. Aloe vera significantly reduced the occurrence of second and third-degree phlebitis. Compared with the control group (50% magnesium sulfate), the total efficacy rate and the cure rate (RR) of Aloe vera group for CIP were 1.29 (95% CI: 1.19-1.39, \(P < 0.001\)) and 2.38 (95% CI: 1.27-4.47, \(P < 0.001\)), respectively. These results suggested that Aloe vera could be used for the treatment of CIP. In conclusion, Aloe vera has some potential clinical value in the prevention and treatment of CIP, but it still needs further study.

Keywords: Meta-analysis, Aloe vera, chemotherapy-induced phlebitis, tumor

Introduction

Intravenous chemotherapy is the most common cancer treatment in clinical practice. However, most chemotherapy drugs can cause phlebitis during the drug infusion. Previous studies reported that the incidence of chemotherapy-induced phlebitis (CIP) in cancer patients ranged from 35% to 56% [1, 2]. CIP not only causes new health hazards for the patients, but also increases the difficulty of venipuncture for nurses, which affects the smooth implementation of chemotherapy. Therefore, clinicians should pay more attention to the issue.

In recent years, Aloe vera, a plant, has been frequently used for the prevention and treatment of CIP in clinical practice. Aloe vera is a stemless or very short-stemmed succulent plant. The leaves are thick and fleshy, green to greygreen. In Chinese traditional medicine, Aloe vera has been used to treat infectious diseases. Nowadays, extracts from Aloe vera are widely used in the cosmetics and alternative medicine industries and marketed as having various rejuvenating, healing, or soothing properties. Some clinical trials have suggested that Aloe vera might be beneficial for the prevention and treatment of CIP. In this study, we performed a meta-analysis, following the preferred...
Aloe vera for chemotherapy-induced phlebitis

Materials and methods

Objectives

The objectives of this meta-analysis were to: i) determine the overall effect of Aloe vera for the prevention of CIP compared with no intervention; and ii) determine the overall effect (the pooled cure rate and effective rate) for the treatment of CIP compared with 50% magnesium sulfate treatment.

Literature retrieval

Searches of the English and Chinese language databases including MEDLINE, EMBASE, the Chinese Biomedical Literature Database (CBM), the China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Full-text Database (VIP), and the Wanfang database were conducted. Search terms included “chemotherapy”, “phlebitis”, “Aloe” and “Aloe vera”. The retrieval deadline was July 31, 2015. After study selection, assessment and data extraction were performed by two reviewers independently, and any disputes were resolved by discussion.

Inclusion and exclusion criteria

Clinical trials about intravenous chemotherapy for tumor patients were included in this study; the intervention group compared Aloe vera for the prevention of CIP to conventional management or to 50% magnesium sulfate (50% MgSO₄) treatment. The outcomes included the incidence of phlebitis and treatment efficiency. The study used Aloe vera or its fresh ingredients such as leaves, juice, and gel; the Aloe vera had not been chemically treated; the method of use was external application (applied to the skin surface over the vein). There was no concomitant application of other drugs or chemicals; and the study used clear criteria for phlebitis. In this systematic review, the grade of phlebitis ranged from 1 to 3 degrees [4].

Studies involving cases of other infusion phlebitis (non CIP), duplicated documents, studies with statistical errors, non-controlled studies, case reports, and case series were excluded from the study.

Quality assessment

The quality assessment was based on the Jadad scale [5]. Randomization, concealment of allocation, blinding of investigators and outcome assessors, and completeness of follow-up were used to determine the quality of the included studies.

Data synthesis and statistical analysis

The Review Manager 5.0 downloaded from the Cochrane Collaboration Web was used for the present meta-analysis. The pooled odds ratio (OR) and relative risk (RR) with the 95% confidence interval (95% CI), heterogeneity (I²), and p-values were calculated across all studies and for each comparison. Simultaneously, tests for heterogeneity were carried out. If significant heterogeneity occurred (P < 0.05), a random effects model was used to calculate a pooled effect size. If the heterogeneity across the studies was not significant (P > 0.05), a fixed-effect model was selected. Publication bias was assessed by funnel plot analysis generated automatically by Review Manager 5.0 software.
A sensitivity analysis was conducted after excluding non-randomized controlled studies.

**Results**

**Overview of included studies**

After a preliminary screen, we selected 218 documents. Some irrelevant studies were excluded after reading the title and summary and 61 studies were initially included in this review. After reading the full text and excluding the studies that did not meet the study criteria, a total of 16 clinical studies [6-21] were included in the present study. The flow chart of study selection is shown in Figure 1. The publication time span of the literature included in this study was 14 years (2001 to 2015), involving a total of 4530 patients (for the preventive management of CIP, experimental group: 2493 cases, control group: 1490 cases; for the treatment of...
CIP, experimental group: 282 cases, control group: 265 cases). According to the Jadad scale, the quality scores of the studies ranged from 0 to 2, suggesting that the overall quality of the included studies was relatively low. The general characteristics of the included studies are presented in Table 1.

Evaluation of the efficacy of Aloe vera for the prevention of CIP

Compared with the conventional method, the overall incidence of CIP in the Aloe vera preventive treatment group was lower. The OR value was 0.13 (95% CI: 0.08-0.20, P < 0.001) (Figure 2). Further subgroup analysis showed that the OR values in 1st, 2nd, and 3rd degree CIP were 0.53 (95% CI: 0.21-1.33, P > 0.05), 0.10 (95% CI: 0.07-0.14, P < 0.001) and 0.10 (95% CI: 0.03-0.34, P < 0.001), respectively (Figure 2), indicating that Aloe vera for the prevention of 2nd and 3rd degree CIP was statistically significant.

Evaluation of the efficacy of Aloe vera for the treatment of CIP

Compared with 50% MgSO₄ treatment (control group), the RR values for the total efficiency rate and the cure rate were 1.29 (95% CI: 1.19-
Aloe vera for chemotherapy-induced phlebitis

1.39, $P < 0.001$, (Figure 4) and 2.38 (95% CI: 1.27-4.47, $P = 0.007$), (Figure 5), respectively.

Sensitivity analysis and publication bias

After excluding non-randomized studies, a sensitivity analysis was carried out. According to the meta-analysis results, the pooled OR of Aloe vera for the prevention of CIP was 0.13 (95% CI: 0.07-0.26, $P < 0.001$), (Figure 6), and the pooled RR values (the overall efficacy rate and cure rate) of Aloe vera for the treatment of CIP were 1.27 (95% CI: 1.17-1.38, $P < 0.001$), (Figure 7) and 2.71 (95% CI: 1.18-6.19, $P = 0.02$), (Figure 8), respectively. Therefore, throughout the sensitivity analysis, the interpretations of the meta-analysis results were consistent. Hence, the stability of this study was acceptable. Based on the evaluation data of the efficacy of Aloe vera for the prevention of CIP, the funnel plot exhibited asymmetry (Figures 9, 10) suggesting this study may be affected by publication bias.

Adverse reactions

No studies reported any adverse reactions, but some studies suggested that allergies might occur among patients susceptible to allergies [7, 10-12], so an allergy test should be carried out before treatment in order to prevent allergic reactions.
Aloe vera for chemotherapy-induced phlebitis

Discussion

Most chemotherapy drugs are alkaloid agents, which can cause non-specific damage to normal cells and tissues while killing tumor cells. The extent of the damage is associated with the cytotoxicity, pH, osmotic pressure, and concentration of the drug [22]. Commonly, cancer patients need to undergo multiple chemotherapies via vein puncture over a short period of time, which can easily cause injury to veins and increase the risk of CIP. In addition, both the tissue repair ability and immune function is significantly decreased in cancer patients, and therefore the patients are prone to developing phlebitis [23, 24].

Conventional treatment for CIP is external applications of 50% MgSO\textsubscript{4}. The mechanism is thought to be as follows: i) 50% MgSO\textsubscript{4} has a hypertonic convergence effect; ii) magnesium ions can protect endothelial cells, increase the synthesis and release of endothelial prostacyclin, enhance anticoagulant activity and inhibit platelet aggregation, improve local circulation and protect the integrity of the blood vessels [25]. However, many studies have shown that using 50% MgSO\textsubscript{4} treatment for CIP has some limitations [26-28]. In recent years, some new methods have been reported to be used for the management of CIP in clinical practice in China [26-31], especially Aloe vera for the prevention and treatment of CIP.
**Aloe vera** for chemotherapy-induced phlebitis

*Aloe vera* is a succulent plant species. A fresh leaf of *Aloe vera* contains a lot of water, aloin, emodin glycosides, isocitrate, plant thrombin, active enzymes, and essential amino acids. These components have the following pharmacological effects [32]: i) soften blood vessels and restore blood vessel elasticity; ii) improve lymphocyte activity and human immunity; iii) dilate blood vessels and promote blood circulation; iv) have antibacterial functions and help to repair damaged tissue; and v) promotes wound healing and cell regeneration. Therefore, theoretically, fresh *Aloe vera* has a therapeutic effect on CIP.

Sixteen clinical trials involving a total of 4530 patients (for the preventive management of CIP, experimental group: 2493 cases, control group: 1490 cases; for the treatment of CIP, experimental group: 282 cases, the control group: 265 cases) were included in this present study. The total sample size is large for the prevention usage, but small for treatment usage. Meta-analysis showed that compared with the conventional method, the overall incidence of CIP in the *Aloe vera* preventive treatment group was low, with the OR value of 0.13 (95% CI: 0.08-0.20). Further subgroup analysis showed that *Aloe vera* for the prevention of 2nd and 3rd degree CIP was statistically significant, indicating that *Aloe vera* can be used to prevent severe and moderate CIP. Compared with 50% MgSO4 treatment (control group), the RR values for the total efficiency rate and the cure rate were 1.29 (95% CI: 1.19-1.39) and 2.38 (95% CI: 1.27-4.47), respectively. The large effect values suggested that using *Aloe vera* for the treatment of CIP instead of 50% MgSO4 can achieve better efficacy and a higher cure rate.

To determine the stability of the meta-analysis, we performed a sensitivity analysis after excluding non-randomized studies. The interpretations of the meta-analysis results were consistent throughout the sensitivity analysis. Hence, the stability of this study is high.

No studies reported adverse reactions, but some studies suggested that [7, 10-12] allergies might occur among patients susceptible to allergies, so allergy tests should be carried out in order to prevent allergic reactions. Allergy test methods were reported in the literature as follows: take a small piece of *Aloe vera* leaf and spread it on the inside skin of the forearm or behind the ear. If the skin turns red, or other symptoms such as itching occur, the treatment should be skipped.

The funnel plot exhibited asymmetry, suggesting this study may be affected by publication bias. In addition, neither the concealment of allocation nor withdrawn nor patients lost follow-up were reported in the included trials. Meanwhile, due to objective conditions, the trials could not implement blinding. According to the Jadad scale, the scores of the studies ranged from 0 to 2, suggesting that the overall quality of the included studies was relatively low. All of these factors limit the validity of the evidence in this study.

In conclusion, we believed that *Aloe vera* has some potential value in the prevention and treatment of CIP, but it still needs further study.
In future, well-designed clinical controlled trials based on the Consolidated Standards Of Reporting Trials (CONSORT) [33, 34] should be conducted in order to scientifically validate the clinical value of Aloe vera for the prevention and treatment of CIP.

Acknowledgements

This work was partially supported by Research Grant from Shanghai Hospital Development Center (No. SHDC12015910).

Disclosure of conflict of interest

None.

Address correspondence to: Changtai Zhu, Department of Outpatient, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, No. 600, Yishan Road, Shanghai 200233, China. E-mail: zct101@163.com; Yongning Sun, Department of Traditional Chinese Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, No. 600, Yishan Road, Shanghai 200233, China. E-mail: yns2002@126.com

References

Aloe vera for chemotherapy-induced phlebitis


