

The effect of *Citrus aurantifolia* (Christm) Swingle on epistaxis as a pre-hospital treatment

Running Title: *Citrus aurantifolia* (Christm) Swingle in epistaxis; home remedy

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Abstract

Objective: Epistaxis is a frequent complaint of emergency ward patients. This study investigated the local effect of *Citrus aurantifolia* (Christm) Swingle (wfo-0001242548). Juice on the control of spontaneous epistaxis in emergency ward patients.

Materials and Methods: This single-blind clinical trial was carried out on 150 patients with epistaxis that referred to the emergency ward. They were randomly assigned into two groups of 75 patients. Cotton soaked in lidocaine and then phenylephrine was used for the control group. Also, cotton soaked in lidocaine and *Citrus aurantifolia* juice was used intra-nasally for the intervention group. The epistaxis control rate was measured.

Results: The epistaxis control rate was 84% in the control group and 37.3% in the intervention group 10 min after the treatment in two groups. The recurrence rate of epistaxis 24 h of follow-up was 14.7% in the control group and 13.3% in the intervention group ($P>0.05$). Also, the complications observed in patients in the two groups were not significantly different. Aggravation of epistaxis, allergy, pain, and burning sensation was present in 6.7%, 4%, and 10.7% of patients in the control group and in 5.3%, 6.7%, and 16% of patients in the intervention group.

Conclusion: The present study suggested that *Citrus aurantifolia* has a mild effect in the treatment of epistaxis, but it was not as effective as phenylephrine in controlling epistaxis; nevertheless, in the first time of epistaxis and mild items, it can be used as an available method at home.

Keywords: Epistaxis; Phenylephrine; *Citrus aurantifolia* (Christm) Swingle, Iranian Traditional Medicine,

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Introduction

Epistaxis is a prevalent complaint among emergency ward clients, so for every 200 visits to the emergency ward, 0.2% will lead to hospitalization. Generally speaking, 60% of patients around the globe will experience epistaxis in their lifetime(1), and 6-10% of cases refer to medical centers. Various methods have been suggested to treat this problem, which are implemented step by step.

The treatments range from local pressure on the soft tissue of the nose to chemical cauterization and angioembolization (2).

Most patients do not consult physicians as soon as epistaxis begins and usually try to control the epistaxis at home with some remedies such as *Citrus aurantifolia* (Christm) Swingle (*C. aurantifolia*) juice known as Key Lime (3) There are many other home remedies for epistaxis in different nations, such as *Notoginseng Radix*, *Bletilla striata*, *Crinis Carbonisatus* (4). Key lime is achievable and pure among Iranian people, so it is used for some purposes, such as as a home remedy for epistaxis in most cases.

C. aurantifolia is a valuable fruit with antioxidant properties that is available in most regions and seasons. Ganiyu et al. in a study demonstrated that lime juice has different properties, such as antioxidant, hypolipidemic, and anti-converting enzyme effects, because of flavonoid content and free radical scavenging potency and ferric-reducing power, so they recommended it for cardiovascular disease treatment. Another study showed that citrus oil is rich in aromatic compounds, namely,

monoterpenes and ketones esters, aldehydes, alcohols such as β -pinene (15.4%), limonene (58.4%), citral (4.4%) γ -terpinene (8.5%), and others (5). The bitter taste and aroma of citrus fruit peels is attributed to limonoids.

The juice of this fruit has highly acidic properties due to the high content of citric acid and ascorbic acid. Lime contains about 88% water, 10% carbohydrates, and less than 1% fat and protein. The amount of citric acid in lime is almost twice that of grapefruit and 5 times that of orange. *C. aurantifolia* is a rich source of citric acid, which contains 1.44 g/oz. *C. aurantifolia* concentrates contain 1.10 g/oz. The citric acid content of commercial lemonade and other fruit juice products varies widely, ranging from 0.03 to 0.22 g/oz(6). (Oz or ounce is a unit of weight equal to one-sixteenth of a pound (avoirdupois); 1 ounce equals 437.5 grains or 28.349 grams).

C. aurantifolia therapeutic properties, according to Chinese or Persian medicine (Iranian traditional medicine), include treating skin disease and gastrointestinal disease and is also used as an epistaxis remedy. Also, it has a metabolic, antiviral, and anti-platelet effect (7).

Effective home remedies reduce healthcare work and hospital congestion. Therefore, the present study investigated the local effect of *C. aurantifolia* juice on controlling spontaneous nosebleeds in patients referred to the emergency.

Methods

This study was conducted as a single-blinded clinical trial. The ethical code is

IR.SSU.MEDICINE.REC.1398.100 and IRCT code is IRCT20180624040228N3. This study was done during 2020 summer in two academic hospitals in Yazd, Iran. The sample size was determined according to similar studies of 150 patients: 75 in the intervention group and 75 in the control group. Random sampling was done among 15 to 55-year-old patients with spontaneous epistaxis who were referred to the emergency room of hospitals. The pharmacologist prepared the medicines (phenylephrine and *C. aurantifolia* juice) and placed them in similar non-transparent containers with coding A and B for each group. Pregnant patients, underlying liver or kidney or heart diseases, people with hereditary and acquired coagulation disorders, patients with nasal anatomy problems (history of Acute trauma, broken and deviated nasal septum), and people with high blood pressure, people with history of malignancy, people with sensitivity to *C. aurantifolia* (and lemon too) or lidocaine or phenylephrine and patients with history of recent trauma to the nose were excluded from the study. All the patients had informed consent.

Preparation of juice: The 10 fresh lemons were washed with tap water, the surface of them sterilized with 70% alcohol, then rinsed with sterile distilled water and opened with a sterile knife and the lemon (8). Juice prepared with pressure out into another sterile container, then the juice filtered (using Millipore 0.45 filter paper) into another sterile bottle to eradicate the seeds and other materials and used freshly without refrigeration. The juice was stored at 3 °C until use, according to a similar study(8). The total amount of the juice was 26 ml.

Patient treatment: Group A was treated with standard treatment with cotton containing lidocaine and then cotton containing phenylephrine (0.5% Nasophrin™).

Group B was treated with cotton containing Lidocaine and then cotton containing *C. aurantifolia* juice. Cotton is dipped in the desired solution according to the nasal cavity volume, using a speculum and bayonet, and completely inserted from the nose floor until the nasal cavity is filled.

The success rate in bleeding control was recorded in a researcher-made questionnaire after 5 and 10 minutes based on the opinion of an emergency medicine specialist who was blind about the type of treatment. The cessation of bleeding from the nose and pharynx (anterior and posterior nostrils) was considered as a response to treatment. In all patients, if there was no response to the treatment, tamponing was performed using a nasal mesh containing tetracycline ointment. Finally, the need for tampons and possible side effects such as sensitivity, pain and burning, increased bleeding, redness, and itching were evaluated in the patients and the results were compared between the two groups. Also, the recurrence rate of bleeding during 24 hours was evaluated using patient telephone calls.

Data analyses

The obtained data was entered into SPSS version 21 software and analyzed with appropriate statistical methods, including descriptive statistics methods (prevalence indices and relative percentages) and appropriate statistical tests (chi-square). A significance level of 0.05 was considered.

Results

Enrollment

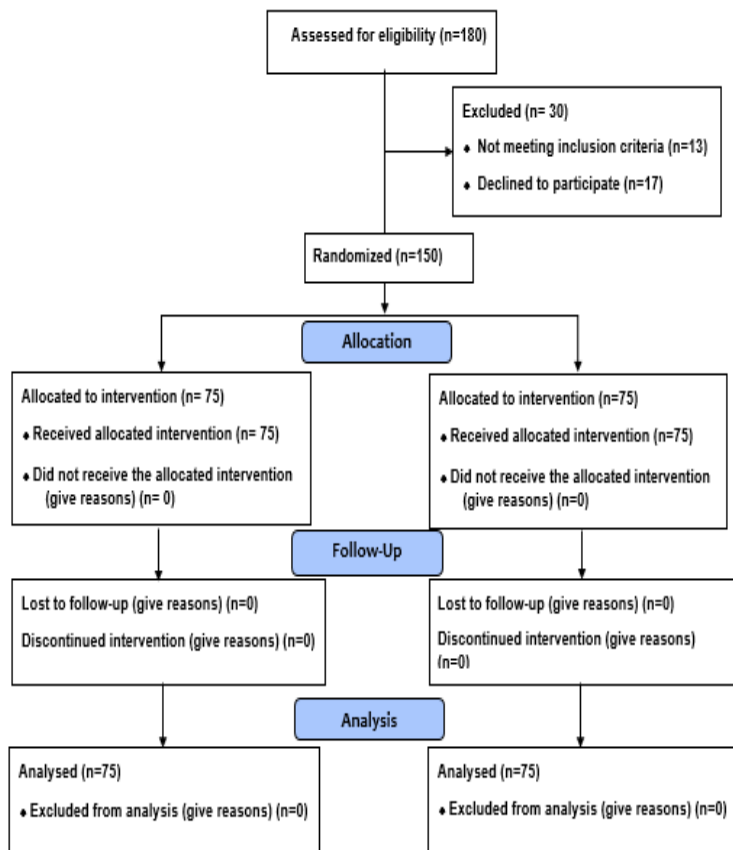


Figure 1. The CONSORT-oriented flow diagram

Fig 1 shows that 180 patients with epistaxis were assessed for the study; 30 patients were Excluded (Not meeting inclusion criteria (n=13) and declined to participate (n=17). In the end, 75 patients were categorized into each group.

Table 1. Frequency distribution of age in people with epistaxis

group	Standard treatment	use of C. aurantifolia juice	p-value
Age, y	35.64 ± 9.14	36.24 ± 8.9	0.68
Gender			
Male	30.70%	36%	0.48
Female	69.30%	64%	

Table 2. Determining and comparing stop bleeding after 5 and 10 minutes and the need for tampon (as an indicator of continued bleeding) in both control (standard treatment) and intervention (use of C. aurantifolia juice) groups

	Stop bleeding after 5minutes	Stop bleeding after 10 minutes	Nasal tampon installed	p-value
Standard treatment*	29(44.1%)	39(46.6%)	7(9.3%)	0.04
use of C. aurantifolia juice	13(17.3%)	46(61.4%)	16(21.3%)	
p-value	0.48			

*Use of cotton containing lidocaine and then cotton containing phenylephrine

Table 3. Determining and comparing the nasal rebleeding after 24 hours between both standard and C. aurantifolia juice treatment groups

Rebleeding After 24 hours	Standard treatment*	use of C. aurantifolia juice	P-value
Yes	11 (14.7%)	10 (13.3%)	0.81
No	64 (85.3%)	65 (85.3%)	

*Use of cotton containing lidocaine and then cotton containing phenylephrine

Table 4. Determining and comparing complications caused in patients in two standard and C. aurantifolia juice treatment groups

Group complications	Standard **treatment	use of C. aurantifolia juice	P-value
Intensification of bleeding*	5 (6.7%)	4 (5.3%)	0.65
Redness and itching	3 (4%)	5 (6.7%)	
Pain and burning	8 (10.7%)	12 (16%)	
No complications	59 (78.7%)	54 (72%)	

* Increased sensitivity in the form of itching, hives, redness, or anaphylactic reaction

**Use of cotton containing lidocaine and then cotton containing phenylephrine

According to Table No1, There is also no significant difference in the distribution frequency of sex in patients (p-value >0.05). There were 30.70% men in this study vs. 69.30% women. The age of the participants in this study was in the range of 20 to 55 years.

The results of the Chi-Square test showed that there is a statistically significant difference (p-value <0.05) between the two groups in terms of epistaxis control and the amount of epistaxis control was higher in the control group (standard treatment) (Table 2).

According to statistical tests, the need for tampons was higher in the group treated with *C. aurantifolia* juice (p-value<0.05) (Table 3).

According to the statistical tests, there is not a significant difference between the two (p-value=0.81), and both groups were similar in their need for tampons after 24 hours (table 3).

The results of the present study showed that the complications experienced by the patients in both groups were similar (p-value=0.65) (table 4).

Discussion

C. aurantifolia has been traditionally used in the treatment and control of epistaxis due to its acidic Vasoconstrictor properties(7); local treatment with vasoconstrictor drugs and nasal electric cauterly is considered as the first, and the use of nasal packs (nasal Tampon) is the second line of epistaxis treatment in the emergency ward (9).

As mentioned, *C. aurantifolia* juice also has an acidotic property and its effect on bleeding control is probably due to this property. The results of the

present study indicated that the control of epistaxis 5 and 10 min after treatment was significantly better in the phenylephrine group than the *C. aurantifolia* group (44% vs. 17.3% after 5 min and 84% vs. 37.3% after 10 min). Furthermore, 9.3% of patients in the phenylephrine group and 21.3% of patients in the *C. aurantifolia* group were treated with tampons due to the lack of control of epistaxis.

Mehryar et al. (2016) studied 120 patients with epistaxis at the Imam Khomeini Educational Center of Urmia. They showed that the administration of 1 cc of tranexamic acid inside a cotton pellet and placing it inside the nose-controlled epistaxis in 66.7% of patients after 10 min, while epistaxis control was achieved after 10 min in 28.3% of control subjects that received phenylephrine. Thus, their study suggested that the parenteral form of tranexamic acid with local injection can be used as an ideal drug to stop epistaxis and lead to a reduction in additional costs and hospital stays in the emergency ward (10).

According to the findings of Mehryar et al., Zahed et al., and our study, local *C. aurantifolia* juice is less effective than phenylephrine in controlling bleeding; it can be concluded that local *C. aurantifolia* juice has a much less effective effect than topical tranexamic acid, so the use of the juice in cases of severe bleeding is not recommended.

The rate of epistaxis recurrence during 24 hours was not significantly different between the two groups. Results revealed that *C. aurantifolia* juice has a short-term effect, so it might be considered a safe medicine. In addition, burning sensation and

pain were more frequent in the *C. aurantifolia* group (10.7% vs. 16%, p-value=0.65).

Even though citric acid is the main ingredient in key lime, the results of the study by Mehryar et al. and Zahed et al. were inconsistent with the present study. The causes may include the following: there is another ingredient in *C. aurantifolia* juice that may interfere with the effect of citric acid and cause it to decrease its effect, the concentration of citric acid is different from those studies, as well as the inclusion and exclusion criteria of the patients in the study. The difference between these two cases suggests that the effect caused by a pure chemical such as citric acid cannot be generalized to plants or fruits containing it, such as key lime, because *C. aurantifolia* contains many ingredients that may interact with each other, and thus diminishing the effect of citric acid.

Another study revealed that *C. aurantifolia* juice has an anticoagulant effect on rats at a 0.4 ml/kg dose. At the same time, there was a notable decrease in fibrinogen concentration. Increased levels of protein C and thrombin-antithrombin complex suggest it helps prevent blood clots and support heart health so this effect may be responsible for our results (11).

Another study on 200 participants revealed that after four months, the dietary lemon supplementation group (2 pieces per day) showed significant improvement in their symptoms, such as gum bleeding and poor wound healing, in contrast with the non-supplementation group. In our study, vitamin C in lemon juice was probably destroyed before topical use, and because of this reason, we

did not observe the same effect as in the above study (12).

Conclusion

The results of the present study show that the topical use of *C. aurantifolia* juice does not improve epistaxis.

Limitation

There is a lack of an objective measurement index for stopping epistaxis in patients.

This intervening variable was controlled as far as possible by trying to double-blind the study, so blinding was not entirely possible in this study.

There is a lack of similar studies to compare the results.

Suggestion

Comparing the effect of *C. aurantifolia* juice with the effect of topical tranexamic acid

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