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Research Article

## EFFECT OF SYZYGIIUM GEL ON ENOXAPARIN INJECTION PAIN IN ACUTE CORONARY SYNDROME PATIENTS

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### Abstract:

*The pain resulting from enoxaparin injection is an undesirable experience that has not yet been effectively controlled in spite of the scientific advances. Therefore, this study aimed to investigate the impact of Syzygium gel on intensity of the pain induced by enoxaparin injection in patients with acute coronary syndrome (ACS). This clinical trial was performed with a crossover design in the Cardiology Department of Farshchian Hospital, Hamadan, Iran. Samples were obtained from the ACS patients through convenience method and assigned randomly into two groups of A and B. Prior to the initiation of the intervention, written informed consent was obtained from the participants. At the first step, intensity of the pain resulting from enoxaparin injection was assessed in both groups following receiving the routine pre-injection cares. Afterwards, as the second step, in group A, 1 cc of clove gel was applied topically in diameter of 3 cm 30 min before the injection, while 1 cc of lubricant gel was used in group B instead of the clove gel. Finally, in the third step, the intervention was swapped between the groups, and the intensity of injection-induced pain was evaluated by visual analogue scale immediately post-injection. The collected data were analyzed using the SPSS, version 16. In the post-injection stage, the mean pain intensities were  $5.95 \pm 1.78$ ,  $5.014 \pm 1.72$ , and  $3.321 \pm 1.52$  in the routine care, placebo, and Syzygium gel groups, respectively, indicating that Syzygium gel application significantly reduced the pain caused by enoxaparin injection ( $P < 0.001$ ). Syzygium gel could be administered by the nurses 30 min prior to enoxaparin injection. It could be considered as an effective and efficient local anesthetic for diminishing site-pain intensity. Furthermore, placebo can assuage pain in case analgesic medications are not available or are contraindicated.*

**Keywords:** Complementary Therapies, Pain, Syzygium, Enoxaparin, Acute Coronary Syndrome.

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**INTRODUCTION:**

Pain is an undesirable sensory and emotional experience resulting from actual or probable tissue injury [1]. Moreover, pain is one of the main patient complaints and 50-80% of the hospitalized patients experience it due to various reasons [2]. Pain leads in discomfort, distress, anxiety, and disability more than any disease [3], and injection is viewed as one of the important causes of pain in hospitalized patients [4]. Experiencing severe pain during injection could undermine patients' trust in nurses' skills, weaken nurses' self-confidence, and cause avoidance behaviors such as non-adherence [2, 5]. Anticoagulants are among the pharmacological agents that induce severe pain during injection and are widely used in acute coronary syndrome (ACS) patients to prevent progression of coronary arteries stenosis [6]. Enoxaparin, which is administered subcutaneously, belongs to this group of medications and is known as an anticoagulant with low molecular weight and long half-life [6, 7]. The known side effects of this agent include pain, irritation, and bruising at the site of injection [8]. In addition to tissue injury due to enoxaparin injection, acidity of the medication exacerbates the pain at the injection site, causing considerable stress in patients [9]. The study performed by Albanese et al. demonstrated that 31.7% and 58.3% of patients receiving enoxaparin 20 mg and 40 mg complained of pain at the injection site, respectively [10]. In addition, it was shown in the study performed by Billon that enoxaparin causes more pain than nadroparin during the first 5 min post-injection [11]. The inevitable side effects of medications should be curtailed and patients' collaboration with therapeutic programs and nurses' competence should be sustained. Moreover, pain management is an ethical commitment for nurses [12-14]. Considering the critical role of enoxaparin in the treatment of ACS patients, non-pharmacological and accessible nursing interventions seem to be essential to prevent and manage the pain caused by the injection of this agent. A review of the literature indicated that various methods have been employed in order to reduce pain at the injection site. These methods include cold and warm compress [3, 15], changing the length and gauge of the needle [16, 17], cooling the needle [18], altering the injection angle [19], and changing the injection duration [5, 6, 9, 20, 21]. Some of the mentioned practices proved to be influential, while some did not show any significant effects. Consequently, other interventions are required for pain management. Application of local anesthetics is one of the cost-effective techniques with low side effects that peripherally inhibit signal transfer from pain receptors. Extract of *Syzygium* plant is among the local anesthetics recommended for

pain relief due to its low price, ease of use, and noninvasiveness [22]. *Syzygium* extract has traditionally been used in aromatherapy in addition to relieving headache, arthritis pain, and toothache [23]. The major constituent of *Syzygium* essential oil (70-80%) is a flavonoid termed eugenol [24]. Flavonoids are considered as a group of nitric oxide synthase inhibitors that exert their analgesic impact through reducing nitric oxide production [25]. Ozgoli et al. demonstrated that aromatherapy with *Syzygium* essential oil diminished labor pain [22]. Khalilzadeh et al. also revealed its impact on control of the corneal abrasion pain and sensitivity in mice [26]. On the other hand, in the study of Kong et al., a *Syzygium*-containing mouth wash did not significantly decrease the pain caused by mucositis in head and neck cancer patients undergoing radiotherapy [27]. In view of the evidence regarding the effects of *Syzygium*, this herb has been recommended for pain relief in traditional medicine [22]. Nonetheless, studies have not evaluated the effects of this herb on different procedures or its application as a local analgesic at the site of injection. Accordingly, we sought to investigate the impact of *Syzygium* gel on the intensity of the pain caused by enoxaparin injection in ACS patients.

**MATERIALS AND METHODS:****Design**

This randomized, double-blind, placebo-controlled, clinical trial with crossover design was performed during February-June 2017 in the Cardiology Department of Farshchian Hospital, Hamadan, Iran. The study samples were selected from the eligible ACS patients.

**Sampling**

The standard sample size was calculated based on a similar study [28]. In this study, the maximum probability of type I error, confidence interval, test power, expected difference for the mean pain intensity ( $\mu_1 - \mu_2$ ), and variance were considered as 5%, 95%, 80%, 1, and 16, respectively. The minimum required sample size was calculated at 45 subjects, which was considered as 50 regarding a 5% probability of attrition.

**The inclusion criteria entailed**

ACS, enoxaparin 80 mg injection twice a day at least for three days, age of 40-60 years, lack of diabetic neuropathy, consciousness, lack of sensitivity to clove, lack of scars or wounds at the site of injection, lack of any pain, except at the site of enoxaparin injection, and none use of pethidine or morphine 4 hours before and during the intervention [29]. The exclusion criteria included unwillingness to

participate in the study, patient discharge, and sensitivity of the patient to clove. The patients who met the inclusion criteria were selected through convenience method, and then they were randomly assigned to groups A and B. To this aim, 70 cards were prepared, 35 of which were written as A and 35 as B. Afterwards, the cards were shuffled and put in a packet and each patient randomly picking a card. The stages of receiving the interventions were also assigned to each group by balloting. We applied a lubricant gel with the brand name of Polygel (Palizteb Shafagh Co., Iran) and clove extract as a topical gel (Ahura Darou, Iran) with eugenol 20% as the effective material (*Eugenia caryophyllata* essential oil).

#### Data collection instruments

A demographic characteristics form including items on age, gender, disease, educational level, and address was completed through self-report. Pain intensity was assessed using the visual analog scale (VAS), the reliability and validity of which for acute, chronic, and cancerous pains were confirmed in various studies [6]. The validity and reliability of this scale were estimated at about 0.76-0.86 and 0.6-0.70, respectively [30].

#### Intervention

Firstly, intensity of the pain resulting from enoxaparin injection was evaluated in the both groups following the routine care and without any additional interventions. Then, in group A, 1cc of clove gel (containing 160 mg of eugenol) was applied in thickness of 3 cm at the injection site 30 min pre-injection [27]. Supportive dressing was used on the area because *Syzygium* contains a significant amount of volatile essential oil [31] and injection was performed after an intended time interval. In group B, the same steps were taken with exception that 1 cc of the lubricant gel was utilized instead of the clove gel. Afterwards, pain intensity was evaluated in both groups. In the next step, the interventions were swapped between the two groups (group A: placebo, group B: clove extract) and injections and pain assessment were performed similar to the previous step.

In order to control for bias and homogenize the comparison and evaluation conditions, all the three injections were executed at 9 a.m. on three consecutive (second, third, and fourth) days of hospitalization. All the injections and interventions were performed by a single researcher. The researcher sterilized 5 cm around the navel in a circular shape by alcohol, and administered the injection in 30 sec [6] at a 90-degree angle without aspirating. It should also be noted that the researcher

did not talk to the patient during the injection and all the injections for the participants were performed in their room and on their bed. The temperature of the injected enoxaparin was 24°C for all the subjects [29]. For each patient, the second injection was on the opposite side. It should also be mentioned that the injection site was not massaged. During the injection, the patients were in supine position with bent knees at a 90-degree angle. The feet were closed and the soles were in contact with the bed surface. A nurse, who had received the required trainings and was blind to the study, assessed and recorded pain intensity immediately post-injection based on VAS. In doing so, the participants were provided a 100-mm ruler and they were asked to mark the injection pain intensity by a pencil; then, the specified number was recorded in the questionnaire. The participants were blinded to type and order of the interventions, and both of the materials were smell-less. Syringes were prepared beforehand to the patients unaware of the interventions.

#### Data analysis

The collected data were analyzed using SPSS, version 16. It is noteworthy that the statistician was also blind to the groups.

#### Ethical considerations

The objectives of this study were first explained to the patients and written informed consent was obtained. The study was approved by the Ethics Committee of Hamadan University of Medical Sciences with the code of IR.UMSHA.REC.1395.452. In addition, it was registered in the Iranian Registry of Clinical Trials with the number of IRCT2017012332129N1.

#### FINDING:

##### Demographic Data

In general, six, one, and two subjects were excluded from the study due to early discharge, transfer to intensive care unit, and enoxaparin hold, respectively. The data obtained from the 70 samples were analyzed and the demographic data of these patients are summarized in Table 1. Furthermore, the results of analysis of variance showed that the mean pain intensity was significantly different between the three study evaluations (Table 2 and Figure 1). According to the results of Tukey's test, the mean pain intensity was significantly different between the groups of placebo and clove gel, placebo and routine care, and clove gel and routine care (Table 3). Furthermore, the results of t-test demonstrated a significant difference between the two genders regarding the mean pain intensity in both lubricant ( $P < 0.019$ ) and routine care ( $P < 0.035$ ) groups. It was indicated that the mean pain

intensity was in the routine care and placebo groups; however, this difference was not statistically

significant in the clove group ( $P < 0.188$ ; Figure 2).

**Table 1: Demographic Characteristics Of The Participants (N=70)**

Demographic Variables		Frequency	Percentage
Gender	Male	25	35.70
	Female	45	64.30
Age(years)	40-45	5	7.14
	46-50	10	14.29
	51-55	19	27.14
	55-60	36	51.43
Wight(kg)	40-60	16	22.90
	61-80	40	57.10
	81-100	14	20.00
Resident	City	48	68.57
	village	22	31.43
level of education	Elementary	41	58.57
	Middle school	17	24.29
	High school	2	2.85
	Diploma degree	7	10.00
	Bachelor's degree	3	4.29

**Table 2: The Table Displays of The Injections Related Pain Scores in Groups.**

Group	N	Mean±(Std. Deviation)	Std. Error	95% Confidence interval for mean		Minimum	Maximum	Sig
				Lower Bound	Upper Bound			
Placebo	70	5.014±(1.72)	0.206	4.603	5.425	1	8	P<0.001
Clove	70	3.321±(1.52)	0.181	2.960	3.683	1	6	
Routine	70	5.950±(1.78)	0.213	5.524	6.376	2	9	

**Table 3: The Table Displays Pairwise Comparisons of Injections Related Pain Scores in Groups.**

Group	N	Mean Difference	Std. Error	95% Confidence interval for mean		Sig	
				Lower Bound	Upper Bound		
Placebo	Clove	70	1.693	0.148	1.397	1.989	P<0.001
	Routine	70	-0.936	0.122	-1.179	-0.692	P<0.001
Clove	Placebo	70	-1.693	0.148	-1.989	-1.397	P<0.001
	Routine	70	-2.629	0.159	-2.946	-2.311	P<0.001
Routine	Placebo	70	0.936	0.122	0.692	1.179	P<0.001
	Clove	70	2.629	0.159	2.311	2.946	P<0.001

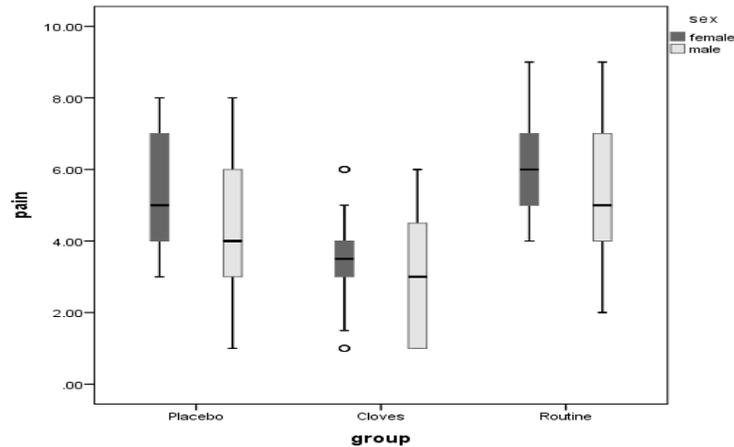


Fig. 1: Bars Display Mean Injections Related Pain Scores in Groups Basis of Gender.

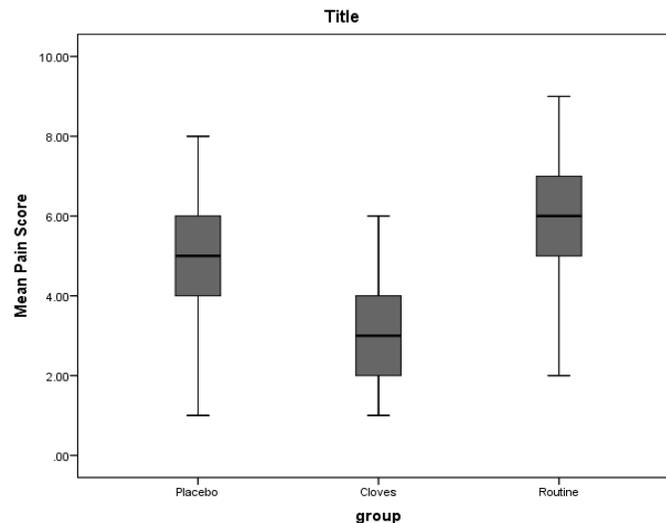


Fig. 2: Bars Display Mean Injections Related Pain Scores in Groups.

### DISCUSSION:

Findings of the present study revealed that Syzygium gel significantly reduced the pain resulting from enoxaparin injection, compared to placebo and the routine care. Although placebo also significantly decreased pain in comparison to routine care, the Syzygium gel diminished the pain intensity more effectively than the other two interventions. Syzygium gel did not cause any dermal or systemic side effects in the current study. Syzygium gel is typically used for relieving toothache [32], and limited studies have investigated its effect on easing injection site pain. The study performed by Alqareer et al. demonstrated that use of Syzygium gel 5 min before inserting the needle into the gum could diminish pain. Results of the mentioned study are consistent with our findings, with the exception that in their study, placebo did not reduce pain in the

subjects [33]. This discrepancy could be due to the fact that placebo was visible at the injection site in our study, which might have psychological impacts. The study conducted by Taher et al. indicated that Syzygium gel could reduce the pain caused by acetic acid injection and contact with hot surfaces in mice, which is in line with the present findings. The difference between our study and the one by Taher et al. was in the route of administration [34]. The mean pain intensity was higher in women than in men; this finding was also reported in another study, indicating that women have a lower pain threshold, compared to men. This difference between the two genders might be due to the anatomical, hormonal, psychological, and social disparities [35]. In addition, the gender of the person who performed the injection might also affect pain expression in men and women. Jesmi et al. conducted a study on 76 patients to evaluate the

effects of EMLA cream on the reduction of the pain induced by enoxaparin injection in coronary heart disease patients. The results of their study demonstrated that topical application of this cream 1 h pre-injection significantly decreased pain during injection. On the other hand, placebo did not diminish pain significantly in the mentioned study. It should be noted that the type of placebo was not specified in their study and the inconsistent results might be due to the placebo type or its route of administration. For instance, the medication in that study was administered by different nurses; thus, blinding might suffer in that study [36]. EMLA is a synthetic chemical agent that is sometimes accompanied by side effects, while *Syzygium* is a medical herb. Our study is methodologically powerful because confounding variables were highly controlled and each person was the control for himself/herself. Furthermore, the intervention time and injection duration were fixed in all the three steps.

#### Limitations

In the present study, we only assessed pain immediately post-injection, while pain may last even for several hours. Therefore, pain assessment over a longer period seems to be essential. Since there is no data on the exact duration of action of this agent after skin absorption, we recommend designing further studies applying the agent multiple times pre-injection. Furthermore, we evaluated the impact of *Syzygium* gel on subcutaneous injection site in the abdominal region, and it would be beneficial to investigate the impact of this gel on other parts of the body and other injection routes. Finally, fear might also play a role in the expression of pain intensity, which is suggested to be controlled in the future studies.

#### CONCLUSION:

*Syzygium* gel is a cost-efficient, available, and non-aggressive herbal product that does not cause serious side effects. Accordingly, nurses can apply *Syzygium* gel as an effective and efficient local anesthetic 30 min before enoxaparin injection in order to reduce site-pain intensity. Pain management increases patient comfort and improves the quality of nursing care services, hence patient satisfaction. Therefore, using pain management agents is recommended in patient care, and even placebo might help in reducing pain intensity.

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#### Conflicts of Interest

None declared.

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