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# Comparison of EMLA and Diclofenac on Reduction of Pain and Phlebitis Caused by Peripheral IV Catheter: A Randomized-Controlled Trial Study

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## Abstract

Peripheral venous catheters (PVC) are often used to provide hydration, medications, and blood products when the length of therapy is expected to be less than one week. Pain and phlebitis are frequent complications of PVC. Diclofenac and EMLA have been used to minimize these adverse effects, however, conflicting results have been reported regarding which has better outcomes. This double-blind, randomized controlled trial was conducted to compare the efficacy of EMLA and Diclofenac (TDP) in attenuating PVC pain and phlebitis. The inpatient setting was chosen because of the higher frequency of PVC insertions, allowing for a sufficient sample size. One hundred fifty-four subjects were randomly assigned to three groups: EMLA patch, a TDP patch, or a patch with lubricant gel as a placebo. The pain was measured by Visual Analogue Scale (VAS). Phlebitis was examined based on Boxtor criteria in intervals of 6, 12, 18, 24, and 48 hours after PVC insertion. The mean score of VAS was  $41.86 \pm 22.49$  for the control,  $39.40 \pm 21.60$  for TDP, and  $38.77 \pm 23.28$  for the EMLA group, with no significant differences in pain severity between the three groups. The rate of phlebitis in the group with EMLA was significantly higher than the other two groups at 6, 12, and 18 hours ( $p=0.02$ ,  $p=0.003$  and  $p=0.04$ , respectively). In all interval times, the rate of phlebitis in the TDP group was significantly lower than the other groups. Compared to men, women experienced higher rate of phlebitis and intensity of PVC pain. EMLA and TDP had similar analgesic effects, but phlebitis was less frequently observed with TDP, suggesting TDP as a potential medication for reducing pain and phlebitis before PVC insertion.

## Introduction

Home infusion therapy has become a common practice in the United States and elsewhere, allowing patients to avoid hospitalization or to be discharged from the hospital earlier (Gorski, 2017; O'Hanlon, McGrail, & Hodgkins, 2017). Peripheral venous catheters (PVC) are often used to provide hydration, medications, and blood products when the length of therapy is expected to be less than one week and the prescribed medication or solution can be safely infused into a peripheral vein (Gorski, 2017). There are complications associated with PVC. They can be minor (pain, catheter occlusions, accidental removals, or major (phlebitis, infection, skin injury, extravasation) (Bugden et al., 2016). Abolfotouh et al. (2014) found the rate of phlebitis in their study to be 17.6%, making it the most common complication of PVC, followed by pain (7.5%). Pain on insertion can cause anxiety, stress, rejection of treatment by patients, and a decline in patients' trust in nurses' clinical expertise (Bond et al, 2016, Agarwal et al., 2008; Akpinar & Celebioglu, 2008; Babaie, 2008).

There are pharmacological approaches for pain control including the use of local anesthetics, and non-steroidal anti-inflammatories (NSAIDs) (Khalili et al., 2014). Each of these has its own advantages and limitations. A combination of lidocaine 5% and prilocaine (EMLA) is the most common analgesic used as local anesthetic on PVC sites. However, EMLA is expensive and less available, particularly in developing countries, which restrict its use as a routine medication for PVC insertion. EMLA has a vasoconstriction property, which causes skin blanching, also known as pallor, that in turn makes IV cannulation more difficult (Agarwal et al., 2008). When the vasoconstrictive effects of EMLA disappear, a generalized local vasodilation occurs, which may lead to erythema and swelling (Tran & Koo, 2014). Blanching, edema, and erythema are not the only side effects of EMLA. Induration (Tran & Koo, 2014),

methemoglobinemia, urticaria, allergic or irritant contact dermatitis, hyper-pigmentation, purpura (Agarwal et al., 2008), and even systematic toxicity (Tran & Koo, 2014) have been also reported following using EMLA.

Another option is NSAIDs such as Topical Diclofenac Patch (TDP) which are available and inexpensive. They are particularly known to be effective for chronic pain through reducing prostaglandin synthesis (Agarwal et al., 2006; Agarwal et al., 2008). Several studies reported the effect of different NSAIDs such as Ibuprofen, TDP, and Piroxicam on attenuating venous cannulation pain (Agarwal et al., 2006; Agarwal et al., 2008; Deshpande & Jain, 2010; Dutta et al., 2003; Khalili et al., 2014). In addition to the analgesic effects of NSAIDs, an anti-phlebitis effect on PVC sites through decreasing platelet aggregation has been reported (Agarwal et al., 2008; Dutta et al., 2003; Predel et al., 2004)

The purpose of this randomized controlled trial was to compare analgesic and anti-phlebitis effects of EMLA cream versus TDP. The aims of are: 1) estimating the pain and phlebitis rates in PVC sites, 2) determining the mean pain score during PVC insertion using the Visual Analogue Scale (VAS) , 3) comparing the pain and phlebitis rates associated with EMLA and TDP following PVC insertion, 4) comparing pain and phlebitis based on the patients' sex.

### **Methods and Materials**

This was a placebo-controlled, double-blind, randomized study. A total of 154 adult patients were recruited from the cardiology and coronary care unit of an educational hospital in Babol, Northern Iran. The inpatient setting was chosen because of the higher frequency of PVC insertions, allowing for a sufficient sample size. This study received IRB and Ethic Committee approval from Babol University of Medical Sciences (BUMS). Informed consents were also

obtained from subjects after explaining the study. Patients who had a non-emergency IV cannulation, and had successful first attempt cannulations were entered in the study. The exclusion criteria were: chronic NSAID use; allergy to NSAIDs or local anesthetics; receiving sedative drugs during the last 24 hours; alcohol/drug dependency or cognitive impairment that could affect patients' ability to rate the pain by VAS; and the presence of scars and eczema on the IV cannulation area.

The sample was randomly divided into three groups. Group one patients (n=61) received an EMLA cream patch (2gm/10cm<sup>2</sup>), group two patients (n=50) received an TDP (Diclofenac 100mg/ 50cm<sup>2</sup>), and group three patients served as the control group (n=43), and received a patch with lubricant gel as a placebo. All TDP and EMLA used in this study were of the same brand and were manufactured in one factory. Patches were administered one hour prior to IV cannulation. Just before insertion of catheters, the sites were wiped off with an alcohol swab and marked by a waterproof marker. Three trained nurses who were blinded to group randomization delivered the intervention. Patients were also blinded to the group to which they were assigned. The patients in the three groups were similar based on their demographic characteristics such as sex and age.

Patches were applied and removed by the first staff nurse who was not further involved in this study. Patches were similar in appearance and unrecognizable by the second senior staff nurse, who would later insert the PC. Intravenous cannulations were performed using 18G cannula and all patients were cannulated on the dorsum of the non-dominant hand. After IV catheter insertion, patients were asked by the senior nurse to immediately rate their pain on a standard non-graduated VAS. This scale is from 0-100 mm (zero meaning not having pain, and 100 meaning maximum pain). The pain score, as rated by patients, was recorded by the nurse.

The signs of phlebitis were also evaluated by the third nurse, according to the Boxter criteria. In this stage, all PVC sites were evaluated for the presence of pain, tenderness, swelling, erythema, and warmth, on the intervals of 6, 12, 18, 24, and 48 hours after PVC insertion. Based on the Boxter criteria, phlebitis was considered positive if at least two of the signs were observed at the cannulation sites.

The software package SPSS18 (SPSS Inc., Chicago, IL) was used for statistical analysis. The frequency analysis (chi-square) test was used to analyze sex ratio. Analysis of variance (ANOVA) was also used for comparing mean for demographic characteristics (such as age), and the mean of VAS in three groups. Phlebitis has also been measured in this study, and since it was on an ordinal scale, a non-parametric test such as Kruskal-Wallis was used for the analysis. A probability value  $< 0.05$  was considered significant.

### **Findings**

Of the 154 participants who were recruited, 77 (50%) were male and 77 (50%) were female. More than 60% of participants had a medical diagnosis of acute coronary syndrome, and their mean hospital stay was  $3.13 \pm 1.46$  days. The mean age was  $64.31 \pm 12.31$  years with the range from 34-88 years. There were no significant differences in demographic variables between the EMLA, TDP, and control group.

All patients (100%) in the control group experienced pain in response to PVC cannulation, compared to 83.6% and 96% of patients in the EMLA and the TDP groups, respectively. However, the mean of the VAS score was significantly decreased in the EMLA and TDP groups compared to the control group ( $86.41 \pm 22.49$  for the control group,  $38.77 \pm 23.28$  for EMLA and  $39.40 \pm 21.60$  for TDP). Intravenous cannulation pain in the EMLA group was lower than the TDP group, but the difference was not statistically significant ( $p=0.77$ ) (Chart 1).

In total 25% of the subjects presented with at least two out of five symptoms of phlebitis on the Boxtor criteria. Comparing phlebitis in three groups showed that the TDP group had the least rates of phlebitis in all measured interval times and EMLA group had the highest rates of phlebitis at hours 6, 12, 18 and 24 ( $p=0.02$ ,  $p=0.003$  and  $p=0.020$ , and  $p=0.027$  respectively) (Table 2). The presence of signs and symptoms of phlebitis were also compared between the three groups. Overall, pain was the most prevalent symptom and erythema was the most prevalent sign experienced by the subjects. In particular, pain was the most frequent symptom of phlebitis in EMLA group at hours 6 and 12, and erythema was the most frequent sign of phlebitis in TDP group at hours 18 and 24 hours. In addition, the average time for phlebitis onset was  $44.22 \pm 11.09$  hours;

There was a significant difference in pain score between men and women ( $p=0.00$ ), in which women reported higher intensity of pain ( $42.07 \pm 21.78$ ) than men ( $37.59 \pm 22.96$ ). In addition, the rate of phlebitis in women was significantly higher than men ( $p<0.02$ ) at different time periods. The mean time of phlebitis was  $40.12 \pm 14.32$  for women and  $48.18 \pm 17.22$  for men ( $p=0.0001$ ).

## Discussion



This study was designed to compare the effects of EMLA and TDP on decreasing pain and phlebitis at the time of insertion and over the 48 hours following PVC cannulation. The findings of this study revealed that EMLA and TDP had similar effects on reducing the pain of IV cannulation, but the phlebitis rate was lower following the use of TDP ( $p < 0.05$ ). Pain and discomfort are common complaints following PVC cannulation. Several studies compared the effect of EMLA and NSAIDs on PVC cannulation pain. These studies used various types of NSAIDs in experimental groups, and a placebo in control groups (Deshpande & Jain, 2010; Dutta et al., 2003; Khalili et al., 2014). In general, they showed the effectiveness of NSAIDs on reducing pain (Agarwal et al., 2008; Deshpande & Jain, 2010; Khalili et al., 2014); however, the degree of effectiveness varies across studies. For instances, in the studies conducted by Deshpande et al. (2010) and Agrawal et al. (2006), TDP decreased the patients' IV cannulation pain to a mild VAS score (VAS < 30mm). Agrawal et al. (2008) found that TDP and EMLA were equally effective in reducing venous cannulation pain that is consistent with the present study.

Other studies revealed different analgesic effect of EMLA and NSAIDs in various times of cannulation. In Dutta et al. (2003), PVC cannulation pain was significantly higher with Piroxicam at insertion time and with cannula advancement, but patients with EMLA had higher scores of VAS at 6, 12, 24 and 48 hours intervals. The Khalili (2014) study revealed that the mean score of VAS in the EMLA group was significantly less than the TDP ( $P = 0.006$ ) that is in contrast with the result of the present study, which did not reach a significant level of difference.

In addition, the results of the current study showed that 83.6 % of patients in the EMLA group, 96 % in the TDP group, and 100 % of patients in the control group, experienced pain during IV cannulation, which is fairly in agreement with Deshpandeh's (2010) findings (62.5% in the EMLA group and 96.6% in the TDP group). Nevertheless, the incidence of pain experience in this study was higher than the rate obtained by Agarwal's 2007 study, (100% in the control group, 37% in the EMLA group, and 48% in TDP group, respectively). Moreover, in the present study the mean score of VAS was  $86.41 \pm 22.49$  for the control,  $39.40 \pm 21.60$  for TDP, and  $38.77 \pm 23.28$  for the EMLA group. Some studies reported the median score of VAS instead of mean. For instance, the Agrawal study (2007) reported the median of pain in the control group was 6, compared to 0 in both the EMLA and TDP groups.

The inconsistency in the mean and rates of VAS scores, and analgesic effects of NSAIDs and EMLA may be related to some variations in research, such as different methodological approaches, study subjects, and the number of participants. For instances, in Dutta et al. (2003), Piroxicam gel and EMLA were randomly applied on the hands of ten volunteers who acted as their own control. A venous cannula was inserted (with no IV infusion) and removed after one hour. In addition, data were collected from healthy volunteers; this means they were less likely to have other underlying debilitating diseases which could affect their feeling of pain. It has been reported that factors such as emotional distress and response to medical treatments influence patients' perception of pain intensity (Jamison & Edwards, 2012; Shankland II, 2011).

The current study showed a rate of 25% phlebitis in all groups that is consistent with the result of the study conducted by Nassaji-Zavareh et al. (2007) with 26% of phlebitis rate. The present study showed that the rate of phlebitis was significantly lower in TDP than two other groups in all measured interval times. This result is consistent with the Dutta et al. (2003) study

that found an NSAID such as Piroxicam gel had more anti-phlebitis effect than the EMLA and the control group, at 6, 12, 24 and 48 hours after cannulation ( $P < 0.01$ ).

Since Boxtor criteria was used for the evaluation of phlebitis, blanching was not examined in our study. However, several studies examined the presence of blanching as an important sign of early stages of phlebitis. For instances, Khalili et al. (2014) revealed that blanching was detected in 20% of subjects with EMLA, but no blanching was seen when using TDP in the experimental group, and vaseline ointment in the control group. The Dutta et al. (2003) study also showed that all subjects had blanching with EMLA at the time of cannulation, and half of the subjects had blanching six hours after cannulation. Occurrence of induration was also more frequent in the EMLA group after six hours. No blanching was found in the NSAIDs (piroxicam) group.

The present study confirmed that sex is an influential factor for the experience of pain, with the mean of VAS in men lower than women. The reason may be due to women having a lower pain threshold and tolerance to pain stimuli (Wandner et al., 2012). In addition, this study showed that women had a higher rate of phlebitis than men. The reason for a higher rate of phlebitis in women is not clear, but hormonal differences between the two sexes may justify this discordance. In agreement with the present study, the Nassaji-Zavareh et al. (2007) study showed that compared to men, women had a higher rate of phlebitis (31% vs. 20.7%).

The findings of our study favor consideration of TDP for reducing IV cannulation pain and phlebitis. However, further studies are needed to discover more protective methods of cannulation, and to improve the understanding of different factors that might influence the risk of pain and phlebitis at PVC sites. For example, in accordance with the hospital policy for critical

care patients, the present study used 18 gauge cannulas on the dorsum sites of the patients. However using a smaller catheters in larger veins may cause different rates of phlebitis and pain intensity. it is well established that larger diameter catheters increase risk of phlebitis.

Given the importance of prevention of infectious and non-infectious complications of PVC as a predictor of quality of nursing care, utilizing the best medication to reduce phlebitis and pain, which are the major and minor sides effects of PVC, is a top priority.

This study was limited by the fact that fluid composition, the volumes of infusion, and the medications infused through the PVC lines were not standardized and were not the same for all patients.

Reducing pain during cannulation can prevent discomfort for patients. Our study showed that applying TDP at the PVC sites, one hour before IV cannulation might be useful for attenuating PVC cannulation pain. Although EMLA has a good effect on decreasing pain resulting from PVC cannulation, it is not significantly more effective than NSAIDs and is even more likely to increase the risk of phlebitis. With respect to the fact that EMLA is more expensive, we suggest that application of TDP at the proposed PVC sites, one hour before IV cannulation, is as an effective and safe method for attenuating IV cannulation pain with minimal local infection.

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Table 1. Demographic characteristic in three groups

| Variables    | EMLA             | Diclofenac       | Placebo       |
|--------------|------------------|------------------|---------------|
| Number (%)   | 61(39.6)         | 50 (32.5)        | 43 (27.9)     |
| Age (yr)     | 63.13 $\pm$ 1.23 | 64.39 $\pm$ 1.12 | 66 $\pm$ 1.39 |
| Gender (M/F) | 31/30            | 25 /25           | 21/22         |

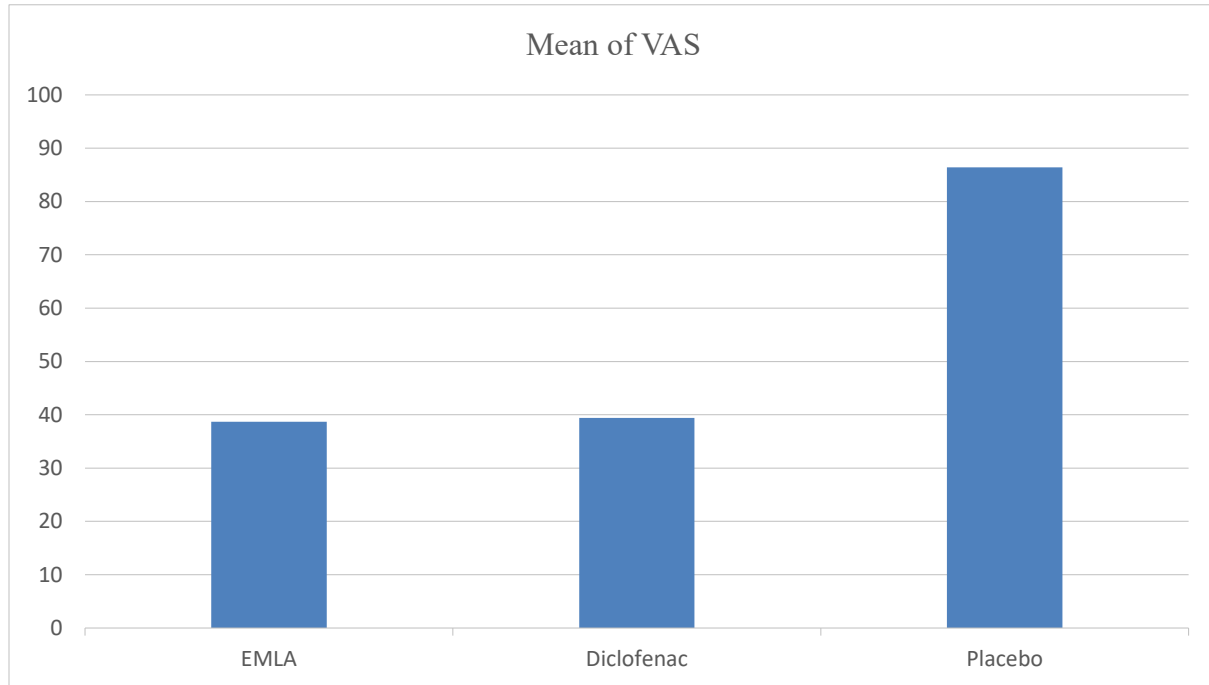
Data are presented as either mean values  $\pm$  SD or by absolute numbers.



Table 2: Comparison of phlebitis in three groups

| Hours<br>Groups          | 6h          |              | 12h          |              | 18h          |              | 24h          |              | 48h          |              |
|--------------------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
|                          | Yes<br>N %  | No<br>N%     | Yes<br>N %   | No<br>N%     | Yes<br>N %   | No<br>N%     | Yes<br>N %   | No<br>N%     | Yes<br>N %   | No<br>N%     |
| <b>Emla</b>              | 9<br>(14.8) | 52<br>(85.2) | 15<br>(24.6) | 46<br>(75.4) | 21<br>(34.4) | 40<br>(65.6) | 30<br>(49.2) | 31<br>(50.8) | 35<br>(57.4) | 26<br>(42.6) |
| <b>Diclofenac</b>        | 0           | 50<br>(100)  | 1 (2)        | 49<br>(98.0) | 6 (12)       | 44<br>(88)   | 17<br>(34)   | 33<br>(66)   | 21<br>(42)   | 29<br>(58)   |
| <b>Lubricant<br/>Gel</b> | 5<br>(11.6) | 38<br>(88.4) | 6 (14)       | 37<br>(86)   | 11<br>(25.6) | 32<br>(74.4) | 18<br>(41.9) | 25<br>(58.1) | 20<br>(46.5) | 23<br>(53.5) |
| P-value                  | 0.02        |              | 0.003        |              | 0.02         |              | 0.027        |              | 0.24         |              |

Chart 1: Intergroup comparison of IV cannulation pain as assessed by a visual analogue scale (VAS).



Data are presented as mean

EMLA = eutectic mixture of local anesthetics