The Effect of Duration of Subcutaneous Injection on the Extent of Bruising and Pain Intensity at Injection Sites among Patients Receiving Enoxaparin Sodium: A Randomized Self-Controlled Clinical Trial

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ABSTRACT

Background: Enoxaparin sodium, in most subcutaneous injections, causes local reactions, such as bruising and pain, at the injection sites. On the other hand, one of the important roles of nurses is safe injection.

Objectives: This study aimed at determining the effect of duration of subcutaneous injection of enoxaparin sodium on the extent of bruising and pain intensity at the patients' injection sites in 2013.

Patients and Methods: In this randomized, self-controlled, clinical trial, 100 patients admitted in two educational hospitals affiliated to Bushehr University of Medical Sciences who were treated with enoxaparin were selected using convenience sampling. For each patient, two subcutaneous injection methods were performed: 10-second subcutaneous injection on the right side of the abdomen as the control group and 30-second subcutaneous injection on the left side of the abdomen as the intervention group. The first injection site was determined using simple random assignment. The bruising area was determined by using computer software 48 and 72 hours after each injection. Also, pain intensity was measured by Numeric Rating Scale (NRS) immediately after each injection. The data were then entered into the SPSS statistical software (v. 21) and were analyzed using non-parametric tests. Statistical significance was set at P < 0.05.

Results: The mean and standard error of bruising in 10- and 30-second injections after 48 h were 45.53 ± 6.35 and 23.69 ± 3.27 mm², respectively. After 72 h, these measures were obtained as 26.45 ± 4.70 and 14.76 ± 3.52 mm², respectively (P < 0.001). Besides, the median and interquartile range of pain intensity scores in 10- and 30-second injections were 5 (4 - 7) and 3 (1.25 - 5), respectively, (P < 0.001).

Conclusions: The results indicated that increasing the length of enoxaparin subcutaneous injection reduced the extent of bruising and pain intensity at the injection sites.

Implication for health policy/practice/research/medical education: Bruising and pain at subcutaneous injection site are two important side effects of enoxaparin sodium that can limit the injection site, cause anxiety, impair patients' mental image, and lead to rejection of the treatment by patients. Application of the results of this study to clinical care will lead to improvement of quality of nursing practice and increase of patient satisfaction and cooperation.

1. Background

Subcutaneous (SC) injection of anticoagulants is a common nursing intervention extensively used to prevent or treat thromboembolism. Among anticoagulants administered via SC injection, injection of low molecular weight heparins, such as enoxaparin, has been increasingly considered (1-4). The results of some studies have indicated that SC injection of enoxaparin resulted in local reactions, particularly bruising and pain at the injection site (5). Bruising induced by enoxaparin injection is usually developed following the...
outflow of blood from the damaged vessels into the SC tissue. This condition usually peaks within 48 hours and starts to decline after 60 - 72 hours (6). As a side effect of injection, pain also causes physiological and psychological discomfort in patients (7). The incidence of pain and its aggravation are the results of two different phenomena. Firstly, the needle is inserted into the skin which stimulates and damages neurons, leading to the feeling of pain (8). On the other hand, sulfate bonds in the drug exacerbate its acidic properties and, consequently, increase the feeling of pain at the injection site (9).

Specialists believe that bruising and pain at the SC injection site are among the major concerns of the patients to whom administration of the above-mentioned drug is essential (6). In this regard, studies have indicated that these complications can limit the injection site, cause anxiety, impair patients’ mental image, result in rejection of the treatment by patients, and decrease patients’ confidence in nurses’ efficiency (5, 10). Researchers believe that factors, such as needle gauge, proper injection site, decreasing the volume of the solution, and the mode of anticoagulants injection, can affect the incidence of bruising and pain at the injection site (11, 12).

A review of the previous studies showed serious concerns about the local complications of SC injection of anticoagulants. In order to decrease the local complications of injecting these drugs, different interventions, such as replacement of the needle before the injection and applying cold before and after the injection, and injection duration were investigated in these studies (5, 10, 11, 13-15). In a study conducted by Rahman et al. on 36 patients who received enoxaparin in Gorgan (northern Iran), no statistically significant difference was observed between the control group (10-second injection) and the intervention group (10-second injection, 10-second pause before needle withdrawal) with regards to bruising and pain intensity (16).

2. Objectives

Despite the importance of prescription of injectable anticoagulants to different patients as well as the impact of undeniable complications of these drugs on patients’ cooperation and treatment continuation, the majority of previous studies have investigated different methods for reducing the complications of SC injection of heparin and few studies have investigated the extent of bruising and pain due to SC injection of enoxaparin sodium. Hence, the present study aims at determining and comparing the extent of bruising and pain in the injection site after SC injection of enoxaparin for 10 and 30 seconds in the university hospitals of Bushehr in 2013.

3. Patients and Methods

3.1. Design, Setting, and Subjects

This randomized, self-controlled, clinical trial was conducted on the patients admitted to the hospitals affiliated to Bushehr University of Medical Sciences. The research population included all the patients admitted to the hospitals affiliated to Bushehr University of Medical Sciences. Besides, the research samples were the patients who were admitted to orthopedic, cardiology, and neurology wards and received enoxaparin as an anticoagulant.

The newly-hospitalized patients with an order of SC injection of 40 mg enoxaparin with the volume of 0.4 or 60 mg enoxaparin with the volume of 0.6 mL during 10 or 30 seconds. For each eligible patient, two methods of 10-second SC injection (Technique A) on the right side of the abdomen (right side of the umbilicus) as the control and 30-second injection (Technique B) on the left side of the abdomen (left side of the umbilicus) as the intervention were performed symmetrically. By referring to the ward, a trained colleague randomly applied technique A or B at the right or left side of the abdomen of each patient (within the radius of 5 cm from the umbilicus) and the other technique was performed 12 or 24 hours later with regard to the instruction of drug administration. The first injection site was determined using simple random assignment. After the patient was determined, the injector opened his/her respective package and performed the injection at one side of the patient’s abdomen. After each injection, a waterproof marker was used to draw a circle with the diameter of 5 cm around the injection site in order to make sure it will not be selected again for the following injection and also to indicate the site for bruising assessment. The patients were instructed not to affect the injection site (itch, touch, and massage).

All the SC injections were performed by a trained co-researcher using a syringe ready for injection with a safety ratchet containing enoxaparin sodium manufactured by Sanofi Co. with a 27-gauge needle and 90 degree angle, without aspiration and by holding the skin of the injection site between the thumb and index finger and injection of 0.2 mL of air as air lock. After injection, alcohol cotton was placed on the injection site for 5 seconds and was then removed without rubbing. Kenko sports chronometer was used to measure the duration of injection.

The primary outcome in this study was the bruising area. Bruising border was transferred to transparent tale by a trained nurse using a CD marker (fin) 48 and 72 hours after

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each injection. Then, its area was determined in millimeter by an expert using a microscope and special software (Image Tool). In order to keep the study blind and avoid bias, the co-researcher administered the injections and a trained nurse specialist measured the bruising border 48 and 72 hours after the injection. It should be noted that while measuring the bruising border, the expert was not aware which injection (10-second or 30-second) was administered at which side of the abdomen.

Pain intensity in both 10- and 30-second techniques was asked from the patients immediately after each injection and recorded using Numerical Rating Scale (NRS). NRS is a horizontal or vertical line showing patients’ perception of pain in a range of numbers from 0 to 10. In this method, zero is no pain and 10 represents the worst and most severe possible pain.

3.3. Data Collection

Data collection lasted from June to December 2013 (seven months). To this end, a researcher-made instrument consisting of three parts was used. In the first section, demographic data (age, gender, education level, medical diagnosis, and ward) were recorded. In the second section, the data on the extent of bruising 48 and 72 hours after the injection using both 10- and 30-second methods were recorded. Finally, in the third section, the data regarding pain severity at the injection site were collected.

3.4. Data Analysis

In order to analyze the data, the bruising area of both interventions was described via mean and standard error and pain intensity was explained using median and percentiles of 25 and 75. Kolmogorov-Smirnov and Shapiro-Wilks tests were used to determine normal distribution of the data. With regard to the fact that the data were not normally distributed and both interventions were made in the same individual, Wilcoxon non-parametric test for matched pairs was used in order to compare bruising and pain severity between the two interventions. Moreover, Spearman correlation coefficient was used to determine the correlation between age, and extent of bruising and pain severity between the two interventions. The results of Spearman correlation coefficient revealed a significant correlation between the extent of bruising and age, in a way that the extent of bruising increased with age. Nevertheless, this test showed no significant correlation between pain intensity and age (Table 3).

4. Results

The participants’ age (n = 100) ranged from 18 to 87 years, with the mean age of 47.78 ± 20.19 years. Additionally, 70 patients (70%) were male and 30 (30%) were female. Furthermore, 62 participants (62%) were orthopedic patients, 31 (31%) were cardiac patients, and 7 (7%) were neurological patients. Besides, 42 patients (42%) were from men’s surgical ward and 27 (27%) were from CCU (Table 1).

The mean extent of bruising was 45.53 ± 6.35 mm² and 26.45 ± 4.70 mm² 48 and 72 h after the 10-second injection, respectively. After the 30-second injection, these figures were 23.69 ± 3.27 mm² and 14.76 ± 3.52 mm², respectively. Comparison of the results of Wilcoxon test on the extent of bruising 48 and 72 hours after the injection showed that the extent of bruising of the 30-second injection was significantly lower than that of the 10-second injection (P < 0.001) (Figure 1). The results also showed that the median and interquartile range of pain intensity scores in 10- and 30-second injections were 5 (4 - 7) and 3 (1.25 - 5), respectively, (P < 0.001).

Pain intensity scores were 2 - 10 after the 10-second injection and 0 - 8 after the 30-second injection. The results of Wilcoxon test showed that the pain intensity of 30-second injection of enoxaparin was significantly lower compared to the 10-second injection (P < 0.001).

According to the results, the extent of bruising 48 and 72 h after 10- and 30-second injections was significantly more in women than in men (P = 0.002). However, no significant difference was found between male and female patients regarding pain intensity in 10- and 30-second injections (P = 0.19, P = 0.84) (Table 2).

The results of Spearman correlation coefficient revealed a significant correlation between the extent of bruising and age, in a way that the extent of bruising increased with age. Nevertheless, this test showed no significant correlation between pain intensity and age (Table 3).

### Table 1. Demographic Characteristics of the Participants (N = 100)

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Diagnosis of patients</td>
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<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Enoxaparin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 mg</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>60 mg</td>
<td>57</td>
<td>57</td>
</tr>
</tbody>
</table>

This research conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Besides, written informed consents for taking part in the study were obtained from all the patients. Additionally, the study was approved by the Research Ethics Committee of Bushehr University of Medical Sciences (B – 92 – 15 - 4) and was registered in the Iranian Registry of Clinical Trials (IRCT201112208473N1).

3.5. Ethical Consideration

This research conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Besides, written informed consents for taking part in the study were obtained from all the patients. Additionally, the study was approved by the Research Ethics Committee of Bushehr University of Medical Sciences (B – 92 – 15 - 4) and was registered in the Iranian Registry of Clinical Trials (IRCT201112208473N1).
5. Discussion

The results of this study showed that 30-second injection decreased injection site bruising and pain intensity compared to the 10-second injection. This might be due to the fact that slow injection reduces the pressure in the injection site, thereby decreasing tissue trauma. In this case, the tissue has a better chance for drug absorption (8). This result has been confirmed in many previous studies (7, 10, 14). However, these studies mainly addressed the adverse effects of unfractionated heparin injection. Conversely, the studies by Chenichek and Rahman et al. on 30-second injection of low molecular weight heparin (enoxaparin) showed no reduction in the extent of bruising (16, 17). Since these studies had a small sample size, the power of their tests in recognition of the possible differences between the injection techniques is subject to doubt. Moreover, the different design of this study (crossover study) decreased the possible influence of the confounding factors.

The findings of the current study demonstrated reduction of pain intensity in the injection site of enoxaparin with 30-second injection compared to 10-second injection. Similarly, the study by Tehrani Neshat et al. indicated that in 30-second SC injection of heparin, the patients perceived less pain compared to 10-second injection (15). Correl considers pain as the result of potential acute tissue injury and believes that increasing the duration of injection can decrease injection-induced cell damage and pain (18). However, the study by Nair showed no statistically significant difference between the 10-second injection control group and the 30-second injection intervention group concerning pain intensity (14). This inconsistency can be due to the differences in the studies’ sample sizes.

### Table 2. Comparison of the Two Injection Methods and Male and Female Patients Regarding Bruising Areas and Pain Intensity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male</th>
<th>Female</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median/IQR</td>
<td>Median/IQR</td>
<td></td>
</tr>
<tr>
<td>Pain intensity</td>
<td>10-second: 5 (3 - 7)</td>
<td>5 (4 - 6.5)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>30-second: 3 (1 - 5)</td>
<td>2.50 (2 - 5)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>SE ± Mean</td>
<td>SE ± Mean</td>
<td></td>
</tr>
<tr>
<td>48h (10-second)</td>
<td>31.70 ± 3.21</td>
<td>77.80 ± 18.72</td>
<td>0.00</td>
</tr>
<tr>
<td>48h (30-second)</td>
<td>16.78 ± 1.87</td>
<td>39.60 ± 9.49</td>
<td>0.002</td>
</tr>
<tr>
<td>Bruising area</td>
<td>72h (10-second): 16.97 ± 2.03</td>
<td>48.56 ± 14.29</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>72h (30-second): 8.04 ± 1.18</td>
<td>30.43 ± 11.02</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* Abbreviations: IQR, Interquartile range; SE, Standard error

### Table 3. The Relationship between Age and Pain Intensity and Bruising Area (48 and 72 h after Injection)

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-second</td>
<td>0.16</td>
<td>0.10</td>
</tr>
<tr>
<td>30-second</td>
<td>0.11</td>
<td>0.24</td>
</tr>
<tr>
<td>48h (10-second)</td>
<td>0.22</td>
<td>0.00</td>
</tr>
<tr>
<td>48h (30-second)</td>
<td>0.24</td>
<td>0.00</td>
</tr>
<tr>
<td>Bruising area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48h (10-second)</td>
<td>0.25</td>
<td>0.00</td>
</tr>
<tr>
<td>48h (30-second)</td>
<td>0.23</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* Abbreviations: r, Spearman correlation coefficients
and the type of scales used to evaluate pain in patients. The present study used NRS since it is easier for patients to use and understand, while Nair used Visual Analogue Scale (VAS) in his study.

In the current study, the extent of bruising was significantly higher in women than in men. The results of some studies in this area have also confirmed that the extent of bruising after the injection of anticoagulants was higher in women compared to men (6, 7). On the contrary, some studies have shown that gender did not influence the incidence of bruising induced by SC injection of heparin (19). The similar results to those of the present study can be explained by the fact that the greater number of blood vessels in women’s skin due to the effect of estrogen can play a role and cause more bleeding in the area damaged by injection (20). However, further studies are necessary to be conducted on the issue.

The results of our study showed a significant relationship between age and the extent of bruising, and that the extent of bruising increased with age. The results of the research by Haldly et al. also confirmed that age had an influence on the extent of bruising in the injection site and older individuals experienced larger bruising at the heparin injection site (21). In the same line, Ebersole believed that collagen tissue decreases by about 1% with age. This could affect the fragility of blood vessels and, consequently, decrease the resistance of the skin and capillary against pressure, easily tearing them. Thus, increased vascular fragility and decreased skin resistance against pressure in the elderly cause larger bruising due to the damages induced by SC injection of heparin (20). The present study results indicated no significant difference in pain intensity based on sex and age. Zebyak et al. also observed no significant differences in pain intensity based on gender and age (7). However, Babaee reported that pain intensity was significantly higher in women compared to men. The reason could be women’s greater susceptibility to nerve transmission of pain and their anatomical and hormonal differences (13).

5.1. Strengths and Limitations
The most important strength of this study was its randomized cross-over design. Since confounding factors are minimized in this type of study due to identical intervention and control groups, causal inferences about the findings are more justifiable. Moreover, a smaller sample size is sufficient for testing the possible effects of interventions. However, the limitation of this study was difficulty in finding the suitable samples for inclusion in this study due to the numerous exclusion criteria.

5.2. Suggestions
The results of this study showed that increasing the time of SC injection of enoxaparin to 30 seconds reduced the extent of bruising and injection pain. Since the extent of bruising is higher in women and the elderly, use of this protocol for enoxaparin injection in these groups can help improve the quality of care and minimize the unpleasant and stressful experience of these patients. Yet, further researches are required to be conducted on the issue.

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Authors’ Contribution
Masoud Bahreini: Study concept and design and critical revision of the manuscript; Afshin Ostovar: study design, analyzing the data, and critical revision of the manuscript; Azar Dadaeen: data collection and preparing the manuscript; Parviz Bazi: data collection and preparing the manuscript; Alireza Raeisi: Preparing the manuscript; Sina Dobarahadan: Preparing the manuscript.

Financial disclosure
The authors declare that there is no conflict of interest.

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