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Effects of cold application before subcutaneous injection of low-molecular-weight heparin on pain, bruising, and hematoma formation: A randomized controlled trial

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ABSTRACT

Aims: With daily subcutaneous low-molecular-weight heparin (LMWH) injections for long periods, there is a high risk of local side effects, such as pain, bruising, and hematoma. This study aimed to compare the impact of cold application on post-injection pain, bruising, and hematoma in patients receiving subcutaneous LMWH following urologic surgery.

Methods: This was a single-blind, randomized control trial. Urology inpatients were randomly assigned to three groups; Group 1: cold application for 2 min before injection, Group 2: cold application for 5 min before injection, and Group 3: control group with no cold application. Post-injection pain was assessed immediately after injection. Bruising and hematoma were assessed at 48th and 72nd hours.

Results: The study included 26 patients in Group 1 (age=63.85±9.89 years; male=84.6%), 26 patients in Group 2 (age=64.54±11.66 years; male=80.8%), and 26 patients in Group 3 (age=65.65±11.36 years; male=88.5%). The pain scores in Groups 1 (11.58±12.06) and Group 2 (6.08±9.11) were lower than Group 3 (28.35±20.97) ($p<0.001$). At the 48th hour, the frequency of bruising in Group 1 (11.5%) and Group 2 (11.5%) was lower than that in Group 3 (38.5%) ($p=0.021$), and the bruise size in Group 1 (4.00±1.73 mm) was lower than that in Group 3 (15.00±7.07 mm) ($p=0.020$). No hematomas was detected in any patient groups at the 48th and 72nd hours.

Conclusions: This study showed that although cold application for 2 or 5 minutes before injection reduced pain and bruising frequency, application for 2 minutes was more effective on bruise size.

Introduction

Side effects, such as pain, bruising, and hematoma, frequently occur following subcutaneous (SC) injection (1). Adverse effects not only result in physical and psychological consequences leading to their reluctance toward subsequent injections but also pose challenges for nurses when selecting injection sites for repeated administrations because of induration and hematoma at the injection site (2-6). Side effects after SC injection are a significant issue, particularly for patients undergoing prolonged anticoagulant therapy (1,6-8).

In the literature, there are various modalities to prevent pain, bruising, and hematoma at the injection site following SC injection, including compression or massage after the injection, application of dry cold or heat, aspiration of the syringe before injection, and slow injection (2,4,5). Among them, cold application is a preventive measure to minimize the effect of SC heparin injections. Moist cold application, dry ice pack, cold gel pack, or vapor cooling spray can be used (9-11). Slowing blood circulation within the targeted tissue cold application exerts several beneficial effects, including curtailing edema and inflammatory responses,

diminishing pain stemming from swelling, regulating bleeding by constraining the capillary surface, inducing local anesthesia by decreasing pain sensitivity, and enhancing coagulation by elevating blood viscosity (1,5,9,11-13).

Some studies indicated no significant effect of cold application on the size and frequency of bruising and hematoma (8,14), whereas others showed benefits (9,12,13,15-20). Despite the lack of effect on bruising and hematoma following cold application, patients' pain perception may has been shown to improve significantly (1,8).

Although many studies have been conducted, most did not report firm conclusions, indicating the need for further studies (5,9,12,20). Particularly, the effectiveness of cold application in reducing pain, bruising, and hematoma following low-molecular-weight heparin (LMWH) therapy and the optimal duration of cold application need to be clarified. Hence, the current study aimed to assess the impact of cold application at varying durations on the incidence of pain, bruising, and hematoma in patients receiving SC LMWH.

Methods

Study design and participants

This single-blind randomized controlled study was conducted from January 2017 to June 2017 on patients who underwent SC LMWH following urologic surgery.

Patients admitted to the urology clinic of a training and research hospital who received postoperative SC heparin treatment were included. The inclusion criteria were age 18 years or older, daily LMWH treatment through a pre-filled syringe containing 40 mg of enoxaparin sodium in 0.4 mL, no visual or auditory impairments, no known coagulation disorders, normal platelets, partial thromboplastin time, and international normalized ratio (INR) values, no hematologic disorder or injury on the abdominal wall, no injections other than enoxaparin sodium at the abdominal site during the study, and willingness to participate in the study. The patients were excluded if they were pregnant, had bleeding at the injection site, experienced pre-existing pain at any body site before injection, presented with conditions such as incisions, drains, scar tissue, lipodystrophy, or infection symptoms at the abdominal site that hindered injection application or were not inclined to participate in the study. This study was registered in the ClinicalTrials.gov Protocol Registration and Results System under the identifier: NCT05771285.

Sample size calculations and power analyses were performed considering the values for bruising reported in a previous study (17). As a reference, it was expected that the bruising area would measure 10.2±5.9 mm in the group without cold application and 6.5±3.1 mm in the group with cold application. Taking a type 1 error of 5% and a type 2 error of 20%, a total of 78 patients were required, comprising 26 patients in the 2-min cold application group, 26 patients in the 5-min cold application group, and 26 patients in the control group. The CONSORT diagram is presented in Figure 1.

The evaluation of bruising and hematoma at the 48th and 72nd-hour post-injection was performed by the same nurse who was blinded to participant grouping.

Randomization

The participants were randomized based on age and gender (14,21,22) using block randomization by stratifying gender blocks into three age groups (www.random.org).

Fifty-five individuals were excluded from the study due to infection, scar tissue, inflammation, incision, or drain at the intended injection site. The remaining patients were categorized into three groups. Group 1 and Group 2 underwent a 2-minute and 5-minute cold application, respectively, at the injection site before injection. Group 3 underwent standardized injection without cold application (Figure 1).

Standard SC injection technique

SC injection was performed by the same researcher following a standardized technique.

- One side of the abdomen was selected 5 cm from the umbilicus.

- After hands were washed, the procedure was explained to the patient, the patient was placed in a semi-fowler position during the injection, the injection site was cleaned with 70% alcohol in circular motions softly outward from the center, and the injection site was left to dry before the injection.

- After drying the area, the skin and SC tissue at the injection site were pinched between the thumb and index finger.

- We used a 25-gauge prefilled LMWH (enoxaparin sodium) syringe with a 1.26 cm needle length and an airlock.

- The needle was inserted into the tissue at a 90° angle, and no aspiration was applied for blood control.

- The injection time of the medication was 10 seconds. Then the needle was withdrawn at the same angle.

- The tissue was pinched between two fingers throughout the injection period and was freed after the needle was withdrawn.

- After the injection process was completed and the needle was withdrawn, dry cotton was pressurized on the injection area. The whitening of the nail edge of the finger exerting pressure was used as the standard of the exerted pressure.

- After exerting pressure with dry cotton, the patient was asked to indicate the severity of the pain felt on the visual analog scale (VAS).

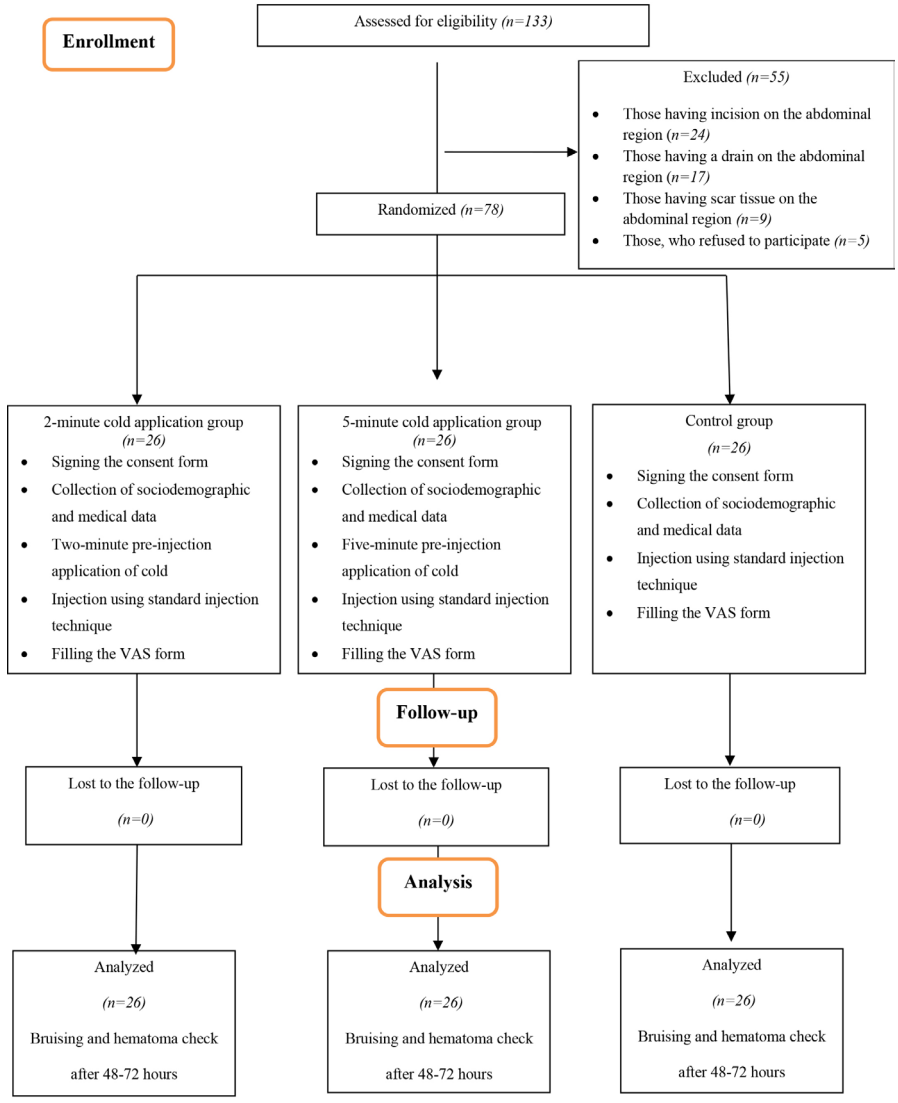

Figure 1. The flow diagram of the study

- After injection, the area was marked with an acetate pen by drawing a circle.

- The patient was informed not to scratch or rub the injection area. No other SC injection or application was made in the area until the assessment of bruising and hematoma at the injection site.

- Other injection areas were chosen when another heparin treatment was needed.

Data collection

We collected sociodemographic and clinical data using a standardized form developed based on relevant literature (1,7,14,16,17,19,23-26). Descriptive characteristics included age, gender, marital status, employment status, and educational background. Prior injection experience, fear of injection, and previous surgical operations were recorded. Body mass index, waist circumference, and prothrombin time with the INR were recorded before the intervention.

A follow-up form was created to systematically document the time and date of injection and monitor pain, bruising, and hematoma at the 48th and 72nd-hours post-injection by the same researcher blinded to the protocol.

We assessed pain and severity using a VAS (VAS, 0-100 mm) (27-29). Immediately after SC injection, patients were asked to mark the severity of pain on a VAS.

A transparent measurement tool, an acetate pen, and millimetric measurement paper were used to measure the bruising size. Adapted from a previous study (18), bruise severity was defined as “bruise present” if color changes were 2 mm or larger, and “no bruise” if color changes were less than 2 mm. At the 48th and 72nd hours after the injection, the injection site was evaluated visually and by palpation for hematoma. A pilot

test was carried out with 5 patients to determine the functionality of the forms. Patients involved in the pilot study were excluded from subsequent assessments.

Outcomes

The outcome measures were between-group differences in VAS score immediately after injection, bruising frequency and size at the 48th and 72nd hours, and hematoma frequency and size at the 48th and 72nd hours.

This study was approved by the Clinical Research Ethics Committee of the Keçiören Training and Research Hospital (decision no: 2012-KAEK-15/1257, date: 11.01.2017).

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to check the normal distribution. Normally distributed variables were expressed as mean±standard deviation, skewed variables as median (minimum-maximum), and categorical variables as number and percentage. Multiple comparisons were performed using the Kruskal-Wallis or ANOVA test for continuous variables and the chi-square test for ratio variables. The significance level was set at $p<0.05$.

Results

The study included 26 patients in Group 1 [age=63.85±9.89 years; male=84.6%], 26 patients in Group 2 [age=64.54±11.66 years; male=80.8%], and 26 patients in Group 3 [age=65.65±11.36 years; male=88.5%] (Table 1). No statistically significant differences were observed among the groups in sociodemographic and clinical characteristics.

Table 1. Sociodemographic and clinical characteristics of the patients in groups (n=78)

Variables	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	Test statistics	p
Age (years) (mean±SD)	63.85±9.89	64.54±11.66	65.65±11.36	0.179*	0.837
Gender, n (%)					
Female	4 (15.4)	5 (19.2)	3 (11.5)	0.591**	0.744
Male	22 (84.6)	21 (80.8)	23 (88.5)		
Marital status, n (%)					
Married	26 (100.0)	23 (88.5)	22 (84.6)	4.080**	0.130
Single	-	3 (11.5)	4 (15.4)		
Educational background, n (%)					
Primary school	17 (65.4)	19 (73.1)	16 (61.5)	2.885**	0.577
High school	3 (11.5)	5 (19.2)	5 (19.2)		
≥University	6 (23.1)	2 (7.7)	5 (19.2)		
Working status, n (%)					
Employed	5 (19.2)	3 (11.5)	4 (15.4)	0.591**	0.744
Unemployed/retired	21 (80.8)	23 (88.5)	22 (84.6)		
Cohabitation, n (%)					
Living alone	-	2 (7.7)	5 (19.2)	7.084**	0.132
Married/not living with his/her children	10 (38.5)	12 (46.2)	11 (42.3)		
Living with a partner and children	16 (61.5)	12 (46.2)	10 (38.5)		
Operations, n (%)					
Prostate surgery	14 (53.8)	16 (61.5)	11 (42.5)	Not assessed	
Kidney surgery	9 (34.6)	-	9 (34.5)		
Bladder surgery	1 (3.8)	10 (38.5)	3 (11.5)		
Testicle surgery	2 (7.7)	-	1 (3.8)		
Other urological surgeries	-	-	2 (7.7)		
BMI (kg/m^2) (mean±SD)	29.69±4.86	28.69±5.09	35.38±30.78	1.021*	0.365
Navel circle (cm) (mean±SD)	105.27±16.04	108.12±14.25	107.69±12.73	0.296*	0.745
Subcutaneous injection experience in the abdominal region, n (%)	6 (23.1)	3 (11.5)	7 (26.9)	2.044**	0.360
Fear of injection, n (%)	8 (30.8)	9 (34.6)	12 (46.2)	1.427**	0.490
PT (mean±SD)	14.50±1.11	14.35±0.79	15.40±2.97	2.355***	0.308
INR value (mean±SD)	1.04±0.14	1.02±0.08	1.11±0.28	1.564***	0.457

Data is represented either as the mean±SD or as the frequency.
*One-way ANOVA, **Chi-square, ***Kruskal-Wallis test was used in comparisons.
SD: Standard deviation, BMI: Body mass index, PT: Prothrombin time, INR: International normalized ratio

Table 2 presents the comparisons of VAS pain scores among the groups. VAS pain scores in Group 1 (11.58±12.06) and Group 2 (6.08±9.11) were significantly lower than those in Group 3 (28.35±20.97) (p<0.001 for both).

Table 3 shows the frequency of bruising among groups at the 48th and 72nd hours following heparin injection. At 48 hours, the frequency of bruising in Group 1 (11.5%) and Group 2 (11.5%) were significantly lower than Group 3 (38.5%) (p=0.021). At 72 hours, there was no significant difference in bruising frequency among the three groups (p>0.05).

Table 4 shows bruise size at 48 and 72 hours. At 48 hours, the bruise size in Group 1 (4.00±1.73 mm) was significantly lower than that in Group 3 (15.00±7.07 mm) (p=0.020). At 72 hours, bruise size was similar between the groups (p>0.05).

We observed no hematomas in any group at the 48 and 72 hours.

Discussion

This study showed that although cold application for 2 or 5 min before injection reduced pain and bruising frequency, a 2-min cold application was superior to a 5-min cold application for reducing bruise size. In addition, no hematoma was detected in the intervention or control groups at the 48th and 72nd hours. SC LMWH injection is commonly performed in nursing practice. Therefore, the results of this study may help guide routine practice to reduce pain and bruising after SC injections. Additionally, we observed no differences among the groups concerning individual factors or medications that could contribute to pain, bruising, and hematoma development following SC injections. In addition, we applied a standardized injection technique to all patients, which can also help decrease the effect of confounding factors and directly reveal the impact of cold application.

Some studies have shown that cold application increases pain tolerance (30-33). Cold exposure decreases catecholamine levels, increases endorphin levels, and delays the transmission of pain signals to the central nervous system, contributing to reduced pain intensity. Pain receptors, which are free nerve endings, are located in the outer layers of the skin. Therefore, acute pain occurs when the needle is inserted into the skin. Cold application interrupts pain perception by affecting sensory nociceptors. It also reduces transmission time and synaptic activities in peripheral nerves. When nerve temperatures decrease, sensory and motor transmission speeds decrease, subsequently preventing the perception of pain is realized

Table 2. VAS pain scores among the groups

	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	χ^2	p
VAS pain score (0-100, mm), mean±SD, median (min-max)	11.58±12.06, 10.00 (0-40)	6.08±9.11, 0.00 (0-25)	28.35±20.97, 20.00 (0-70)	21.661	**<0.001**[a,b]

χ^2: Kruskal-Wallis test. [a]: Comparison between 2-minute cold application group and control group, [b]: Comparison between 5-minute cold application group and control group.
VAS: Visual analog scale, SD: Standard deviation, min-max: Minimum-maximum

Table 3. The frequency of bruising at 48th and 72nd hours by groups (n=78)

The frequency of bruising	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	χ^2	p
48th hour					
No bruise (<2 mm), n (%)	23 (88.5)	23 (88.5)	16 (61.5)	7.706	**0.021**[a,b]
Bruise present, n (%)	3 (11.5)	3 (11.5)	10 (38.5)		
72nd hour					
No bruise (<2 mm), n (%)	24 (92.3)	23 (88.5)	21 (80.8)	1.606	0.448
Bruise present, n (%)	2 (7.7)	3 (11.5)	5 (19.2)		

χ^2: Chi-square test, [a]: Comparison of 2-minute cold application group and control group, [b]: Comparison between 5-minute cold application group and control group

Table 4. Bruise size at 48th and 72nd hours by groups

	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	χ^2	p
Bruise size (mm) at 48th hour, mean±SD, median (min-max)	4.00±1.73, 5.0 (2-5)	10.00±5.00, 10.0 (5-15)	15.00±7.07, 10.0 (10-30)	7.805	**0.020**[a]
Bruise size (mm) at 72nd hour, mean±SD, median (min-max)	4.00±1.41, 4.0 (3-5)	24.33±22.50, 15.0 (8-50)	15.60±9.32, 10.0 (8-30)	4.476	0.107

χ^2: Kruskal-Wallis test, [a]: Comparison between 2-minute cold application group and control group.
SD: Standard deviation, min-max: Minimum-maximum

(1,8,9,11,15,34,35). In this study, the groups subjected to cold application demonstrated lower pain scores than the groups not subjected to cold application. This can be explained by reduced pain perception due to the physiological effects of cold application. Similar to our results, many studies have reported that pain perception decreased in patients who received cold application before SC LMWH injection (1,8,19,20).

In this study, we observed a significant increase in the frequency of bruising in the control group that did not receive cold treatment. Cold application reduces skin and SC tissue temperatures, resulting in vasoconstriction. The vasoconstrictive response initially occurs through direct action and subsequently through a reflex mechanism. When a person is exposed to cold, alpha (α) receptors that modulate vasoconstriction are stimulated by the sympathetic nervous system, leading to vasoconstriction and diminished blood flow to the affected area. Reduced transportation of oxygen and other metabolites to tissues and elimination of waste products ultimately slow down tissue metabolic processes. Thus, the reduction in blood flow induced by vasoconstriction forms the fundamental rationale for cold application to control hemorrhage (11,30,36,37). The reduction in bruising observed in the intervention groups can be attributed to the aforementioned physiological effects of cold application.

Another important result of this study is that the physiological effects of a 2-minute cold application may reduce bruise size. Additionally, although not statistically significant, an increase in bruise size was observed in the 5-minute cold application group compared with the 2-minute cold application group. The influence of cold on blood vessels initially triggers vasoconstriction, but if the skin temperature drops excessively, this vasoconstriction gives way to vasodilation. Vasodilatation reduces the effect of cold at the cellular level (36). Several studies indicated that blood flow tends to decrease after 5 minutes of cold application and further decreases with prolonged applications. However, over time, the body initiates a response known as the “Hunting Reaction” leading to increased skin blood flow to warm the cold tissue (11,38,39). Increased bruise size observed in the 5-minute cold application group compared with the 2-minute cold application group can be explained by the transition from vasoconstriction to vasodilation to increased body temperature and the potential enlargement of bruises due to increased tissue perfusion (39). However, further studies are required to address this issue.

In this study, no hematoma was detected in any groups at 48 and 72 hours. Before commencing the study, we thoroughly reviewed the literature and developed a standardized injection technique for SC LMWH administration that was consistently applied to all patients. The absence of hematoma in the group that did not receive cold application suggests that the standardized injection technique can effectively prevent hematoma. Kuzu and Ucar (1) also concluded that standardized injection technique was an important factor in hematoma prevention.

In this study, participants were randomly selected taking into account factors such as age and gender that were considered to induce pain, bruising, and hematoma at the injection site. In addition, bruising and hematoma assessment was performed by a nurse who was unaware of the method used. This increases the reliability of the study.

The participants were administered only one SC LMWH injection, and the results were limited to the applications to the abdominal region. Furthermore, future studies with different injection sites and number of injections are required.

Conclusion

In conclusion, this study showed that 2 and 5 minutes of cold application before SC LMWH injection effectively reduced pain and bruising frequency, but 2 minutes of cold application was more effective than 5 minutes in reducing bruising size.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the Keçiören Training and Research Hospital (decision no: 2012-KAEK-15/1257, date: 11.01.2017).

Informed Consent: Written informed consent was obtained from each participant.

Authorship Contributions

Concept: C.İ.B., F.İ.Ç., Design: C.İ.B., F.İ.Ç., Data Collection or Processing: C.İ.B., Analysis or Interpretation: C.İ.B., F.İ.Ç., Literature Search: C.İ.B., F.İ.Ç., Writing: C.İ.B., F.İ.Ç.

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